Enhanced Recovery After Surgery – ERAS in Elective Craniotomies-a Non-randomized Controlled Trial

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Abstract

Background: Enhanced Recovery After Surgery (ERAS) is a multimodal perioperative care bundle aimed at early recovery of patients. Well accepted in gastric and pelvic surgeries, there is minimal evidence in neurosurgery and neurocritical care barring spinal surgeries. We wished to compare the length of intensive care unit (ICU) or high dependency unit (HDU) stay of patients undergoing elective craniotomy for supratentorial neurosurgery: ERAS protocol versus routine care. The secondary objective was to compare the postoperative pain scores, opioid use, glycemic control, and the duration of postoperative hospital stay between the two groups.

Methods: This was a pragmatic non-randomized controlled trial (CTRI/2017/07/015451). Consenting adult patients scheduled for elective supratentorial intracranial tumor excision were enrolled prospectively after institutional ethical clearance and consent. Patients in the ERAS group received a fixed bundle of care. Pre-operative – family education, complex-carbohydrate drink, scalp blocks, and flupiritine; Intraoperative – limited opioids, fluid and temperature regulation; Post operative- early mobilization, removal of catheters and initiation of feeds. In the control group, standard practice and protocols of perioperative care were followed. The two groups were compared with regards to the length of ICU stay, pain scores in ICU, opioid requirement, glycemic control and the overall duration of stay in the hospital.

Results: Seventy patients were enrolled. Baseline demographics – age, sex, tumor volume and comorbidities were comparable between the groups. The proportion of patients staying in the ICU for less than 48 hrs after surgery, the cumulative insulin requirement and the episodes of VAS scores > 4 in first 48 hours after surgery was significantly less in the ERAS group – 40.6% vs 65.7%, 0.6 (±2.5) units vs 3.6 (±8.1 ) units and 1 vs 10 episodes (p= 0.04, 0.001, 0.004 respectively). The total hospital stay was similar in both groups.

Conclusion: The study demonstrated a significant reduction in the proportion of patients requiring ICU/ HDU stay > 48 hrs. Better pain and glycemic control in the postoperative period may have contributed to a decreased stay. More extensive randomized studies may be designed to confirm these results.

Background

Enhanced Recovery After Surgery (ERAS) is a multimodal perioperative care pathway that has led to a dramatic change in the conventional surgical doctrine. Its implementation has demonstrated success in early rehabilitation and shortened duration of the hospital, and Intensive Care Unit (ICU) stay for postoperative patients undergoing elective gastroenterological, urological, obstetric, and oncological surgical procedures. (1)(2)

ERAS protocols target perioperative stress response with specific goal-directed evidence-based practices. (3) In recent times, each surgical discipline has been developing modifications of ERAS protocols to improve patient compliance and achieve better surgical results. Decreased wound infection, faster healing, early boweland bladder recovery, shorter duration of ICU, and hospital stay have reduced the
Based on the established success of ERAS protocols in other surgeries, Hagan et al. in 2016 proposed a set of seventeen evidence based practices that could be prospectively applied to cater to neurosurgical patients and called upon the necessity of undertaking prospective studies to establish feasibility and success in this field. Since then, there have been very few studies reporting successful use of ERAS in nonspinal neurosurgery.

Here, we describe the use of a modified, multidisciplinary ERAS protocol for elective supratentorial surgeries. We aimed at studying the effect of the modified ERAS protocol on patients of elective supratentorial tumor surgeries- post operative duration of ICU stay, pain control, analgesic requirement, glycemc control and hospital stay.

**Methods**

**Design and Study Centre**

Our study was a prospective non-randomized trial conducted in an 800 bedded tertiary care teaching center having super-specialty courses in neuroanesthesia and neurocritical care. The institute has a dedicated neuro ICU with 24-hour coverage by trained intensivists. At the time of this study the area had a combination of 8 ICU and high dependency beds (HDU), and henceforth we use the term ICU to refer to any of these bed types. The study was granted permission by the institute ethics committee (IEC) and was prospectively registered. Informed consent was obtained from all patients before participation in the study, and the trial was registered prospectively with the Indian clinical trials registry (CTRI/2017/07/015451). A change in the type of study design (as suggested by our institute ethics committee) lead to re-registration with the trial registry retrospectively and a new registration number was given (CTRI/2018/04/013247).

**Patient recruitment**

All adult patients of ASA physical status I and II over the age of 18 years (inclusive), with a single supratentorial space-occupying lesion posted for elective craniotomies were included. Moribund patients requiring emergency craniotomies, uncontrolled diabetics, severely cognitive impaired patients unable to follow simple instructions, and those who did not consent were excluded. After obtaining informed consent for participation, all patients and their family members were explained about the study. Those who understood and agreed to follow and adhere to the new ERAS protocol were included in the trial. The rest served as controls.

**ERAS protocol Vs. Conventional Care**

An ERAS protocol bundle, based on the existing literature and that proposed by Hagen et al., was agreed upon by the Department of Anesthesiology and Critical care and the Department of Neurosurgery in conjunction with the Critical care nursing and dietetics divisions and approved by the institutional ethics committee (vide approval No. IEC/AIIMS BBSR/PG THESIS/2017–
The protocol consisted of primarily three segments – Pre-operative, intra-operative, and postoperative. (Fig. 1)

The pre-operative ERAS bundle began in Group ERAS (GrE) with a structured pre-operative counseling and education. The patients and next of kin were informed about the elements of care of the multimodal ERAS protocol. An active patient and caregiver participation was encouraged to improve compliance. All patients in GrE received a pre-operative complex carbohydrate maltodextrin drink (Preload→) 100 grams in 200 mL of clear water the night before surgery, and repeated 50 grams in 100 mL water 2 hours preceding the surgery. (7)

All the patients received pre-emptive analgesia (flupiritine maleate) 100 milligrams the night before surgery, repeated 2 hours before surgery. (8) The control group (GrC) did not receive the elements of care as mentioned above, and standard pre-operative fasting guidelines were followed.

Induction and maintenance of anesthesia were standard for both the groups with intravenous propofol (titrated to loss of verbal response), short-acting opioids (fentanyl – 2 mcg/kg bodyweight.), vecuronium (0.1 mg/kg body weight) and isoflurane titrated to minimum alveolar concentration (MAC) of 1-1.5. After induction, all GrE patients received scalp blocks with 20 mL 0.25% Bupivacaine. The Anaesthesia team performed the scalp block. Incision site infiltration with lignocaine 2% (10 mL), second hourly sugar monitoring, goal-directed fluid therapy, and intra-operative temperature monitoring were done for both the groups. In addition to these measures, a nasogastric tube was placed in all Gr E patients.

**Outcome Measures**- Patients with a duration of ICU stay of < 48 hours, defined as the number of calendar days from ICU admission to the time of discharge from the ICU were recorded for each group as the primary outcome measure. The secondary measures were total episodes of visual analogue score (VAS) > 4, insulin (Units) and fentanyl (micrograms) administered in the first 48 hours of ICU stay, and the total duration of hospital stay after surgery.

In the postoperative period, second hourly pain assessment (VAS) and eighth hourly glucose monitoring were done for the first 48 hours of ICU stay or till discharge from ICU whichever was earlier. In addition to intravenous paracetamol (1 gram) given three times daily to both the groups, all Gr E patients received 100 mg of Flupiritine Maleate three times a day through their nasogastric tubes. Early enteral feeding was started for all Gr E patients within the first 6 hours of ICU admission, provided there were no contraindications (such as an anticipated relook surgery). The decision for enteral feeding was delayed until after the first successful extubation trial in the GrC as per unit protocol. Opioids were avoided in the postoperative period in both the groups, to be used as rescue analgesia if the VAS score was > 4. Foley’s catheter and surgical drains were removed on the first postoperative day for all Gr E patients as a part of the ERAS protocol. The decision for removal of indwelling catheters was left to the surgical team in Gr C. Patients in GrE who developed urine retention, or developed syndrome of inappropriate antidiuretic hormone secretion (SIADH) could be recatheterized on a case to case basis.
Postoperative mechanical ventilation was a combined decision of the anesthesia and surgical teams, and the sedation protocol for these patients was similar for both groups of patients—involving an infusion of dexmedetomidine as the agent of first choice. Postoperative sugar control was strictly maintained through eighth-hourly glucose monitoring for both the subset of patients. Patients whose blood glucose levels were above 180 mg % were restarted on an insulin infusion with second-hourly monitoring as per our institutional practice titrated to maintain between 120–180 mg%. Patients who were conscious and weaned off the ventilator and vasopressor support were ambulated or sat out of bed (for patients with hemiplegia/paresis) on the first postoperative day. This practice was standard of care and was followed for both sets of patients.

**Discharge**

The decision of discharge from the ICU was taken by the dedicated ICU team for both subsets of patients and decided after the combined neurosurgical and critical care team agreed. Discharge criteria were same for both groups, and included adequate pain control, afebrile state, cardiopulmonary stability, and being able to sit out of bed. Both subsets of patients were followed up till the day of discharge from the hospital.

*Adherence*; To maximize adherence, an ERAS checklist was attached to all eligible patients after obtaining consent. Before starting the study, a workshop was organized to train the nursing teams of both intensive care units and neurosurgery ward to familiarize the staff and resident doctors with the various elements of the ERAS protocol—this module was repeated twice during the study period to cater to changes in staff-mix.

**Data Collected**

Patient demographic data such as age, sex, body weight, ASA physical status, type and volume of the tumor, a pre-existing comorbid illness like hypertension, hypothyroidism, and diabetes mellitus were recorded in the patient data form. The total episodes of VAS scores above four, cumulative insulin administered during 48 hours of ICU stay, and the total duration of hospital stay were recorded. Also, the dose of fentanyl used as rescue medication, and the incidence of any postoperative complications were recorded. The same experienced surgical team operated all the patients of both subsets. All patients received their allocated interventions.

**Statistics**

The sample size calculation was based on data obtained from the medical records of the previous six months. Seventy percent of patients operated for supratentorial tumors by the same surgery and anesthesia team had postoperative ICU stay of >48 hours. It was hypothesized that the ERAS protocol
could bring this down by 50%. For a 80% power, an alpha error of 5%, and 10% attrition, a sample of 70 patients would be needed.

Descriptive statistics were used to compare the patient baseline characteristics. All continuous data which were normally distributed were analyzed using Student's t-test, whereas nonparametric data were analyzed using the Mann – Whitney U test. A chi-square test or Fisher’s exact test was used for qualitative variables. All the statistical tests were performed using the SPSS software, version 25.

**Results**

A total of 108 patients were eligible of which 14 patients were excluded for lack of consent. Twenty four patients (11 in Gr E and 13 in Gr C) were excluded after consent due to logistic reasons such as operation theatre unavailability on the day of surgery. Patients were recruited between August 2017 to October 2018 and the follow-up was completed by end of November 2018. Figure 2.

The baseline demographic characteristics were similar between the two groups (Table 1). The median duration of surgery, intraoperative fluids, urine output, blood loss, and temperature were comparable between the two groups. The primary indication for surgery did not differ between the groups — the majority of the patients presented with meningiomas, followed by gliomas and craniopharyngiomas. The tumor volume was assessed by the 3-D reconstruction of the CT scans during the pre-operative period and was similar between the groups. The intra-operative parameters have been summarized in Table 2.
Table 1
Baseline characteristics of 70 patients

| Parameter                | ERAS group (GrE) | Control group (GrC) | p value | CI         |
|--------------------------|------------------|---------------------|---------|------------|
| No. of patients          | 35               | 35                  |         |            |
| Age in years             | 40.89 ± 13.61    | 46.89 ± 13.95       | 0.07    | -0.57–12.57|
| Body weight in Kg        | 58.66 ± 7.3      | 60.0 ± 6.82         | 0.43    | -2.03–4.71 |
| Sex                      |                  |                     | 0.81    |            |
| Males                    | 14(40%)          | 16(45%)             |         |            |
| Females                  | 21(60%)          | 19(55%)             |         |            |
| ASA Classification       |                  |                     | 1.0     |            |
| ASA I                    | 26               | 26                  |         |            |
| ASA II                   | 9                | 9                   |         |            |
| Co-morbid illness        |                  |                     |         |            |
| Hypertension             | 8                | 6                   | 0.76    |            |
| Diabetes Mellitus        | 1                | 3                   | 1.0     |            |

(Values have been described in terms of means ± SD for parametric data and medians (range) for non parametric data)
| Parameter                              | **ERAS group (GrE)** | **Control group (GrC)** | **p value** | **CI**          |
|---------------------------------------|----------------------|-------------------------|-------------|-----------------|
| No. of patients                       | 35                   | 35                      |             |                 |
| Nature of tumor                       |                      |                         | 0.72        |                 |
| Meningioma                            | 19                   | 22                      |             |                 |
| Glioma                                | 10                   | 9                       |             |                 |
| Others                                | 6                    | 4                       |             |                 |
| Duration of surgery (in minutes)      | 253.14 ± 72.03       | 283 ± 91.83             | 0.14        | -9.51 – 69.22   |
| Intra-operative blood loss (mL)       | 824.57 ± 518.01      | 711.43 ± 463.06         | 0.34        | -347.5 – 121.21 |
| Intra-operative crystalloid (mL)      | 2298.57 ± 552.47     | 2375.71 ± 777.28        | 0.63        | -244.51 – 398.79|
| Intra-operative temperature (°F)      | 98.69 ± 0.72         | 98.77 ± 0.82            | 0.65        | -0.28 – 0.45    |
| Tumor volume (mL)                     | 45.2 (1090.9)        | 45.0 (1143.2)           | 0.70        |                 |
| Packed RBC volume (mL)                | 240 ± 347.64         | 190 ± 353.51            | 0.55        | -217.23 – 117.23|
| Urine output (mL)                     | 685.14 ± 393.58      | 633.14 ± 321.31         | 0.55        | -223.37 – 119.37|
| Intra-operative random blood sugar (mg%) | 127.83 ± 19.81      | 152.17 ± 38.73          | 0.02*       | 3.67 – 45.00    |

(Data has been represented as means ± SD or medians (range) and appropriate statistical tests have been used)

Number of patients staying in ICU/HDU for more than 48 hrs was significantly lesser in the ERAS group of patients than in Control group. ($\chi^2$ (1, 70) = 8.571, $p = 0.003$) The absolute risk reduction was 25.02% (number needed to treat = 4, CI = 2.1 – 52.1), which showed that one out of every four patients benefitted from the ERAS protocol with a reduced duration of ICU stay.

Out of 35 patients in Gr E, 21 (60%) had their urinary catheters removed on the first postoperative day against 13 in Gr C. Of the 14 in Gr E whose catheters were not removed, 9 had SIADH.

There was a significant difference in the insulin administered to the groups - Gr C required a higher cumulative dosage of insulin within the first 48 hours after surgery (Median 0, range 35 Units) than the ERAS group (Median 0, range 12.5 units) ($U = 486.00, p = 0.03, r = .25$).
Postoperative pain scores showed a significant difference between the groups. Twenty eight out of 35 patients in ERAS did not have even one episode of VAS above 4 in the first 48 hours of ICU stay compared to 19 in the control group. \( (X^2 \ (3,70) = 9.79, p = 0.02) \)

The cumulative fentanyl dose in ERAS group (Median 50, range 100 mcg), was significantly lesser as compared to control group (median 50, range 300 mcg) \( (U = 438.50, p = 0.02, r = .27) \)

The mean duration of post-operative hospital stay was not different between the two groups (Table 3).

Table 3

| Parameter                                      | ERAS group | Control group | p value | CI        |
|------------------------------------------------|------------|---------------|---------|-----------|
| No. of patients                                | 35         | 35            |         |           |
| Number of patients staying more than 48 hours in ICU | 15         | 27            | 0.003*  |           |
| Mean duration of post operative hospital stay (days) | 11.49 ± 9.04 | 12.08 ± 8.76 | 0.78    | -3.65–4.84 |
| Cumulative insulin dose (units)                | 0 (12.5)   | 0 (35)        | 0.03*   |           |
| Episodes of VAS >4 in the first 48 hours of surgery | 28         | 19            | 0.02*   |           |
| 0                                              | 7          | 8             |         |           |
| 1                                              | 0          | 7             |         |           |
| 2                                              | 0          | 1             |         |           |
| 3                                              | 2          | 3             | 0.6     |           |
| Death / Mortality                              | 2          | 3             |         |           |
| Cumulative fentanyl dose (mcg) in first 48 hrs | 50(100)    | 50 (300)      | 0.02*   |           |

Data has been represented as means ± SD or median (range) or proportions wherever appropriate.

The ERAS group of patients did not exhibit any complications related to the implementation of the protocol.

**Discussion**

There is limited evidence for the benefit of an ERAS protocol in neurosurgery patients. We show in this study, that implementing a multidisciplinary ERAS protocol suited for craniotomy patients is feasible and may reduce the proportion of patients requiring a longer ICU stay significantly. We also demonstrate possible associations with specific components of the protocol responsible for this improvement in the
outcome- decreased pain, less requirement of opioids after surgery and better glycemic control, and earlier mobilization.

At the time our study was initiated in early 2017, there was no evidence that ERAS protocols could be modified and used for neurosurgery patients. A set of suggested guidelines based on non-neurosurgical evidence was presented by Hagan et al., which, although intuitively attractive, would need evidence to be applied to craniotomy patients. ERAS guidelines for spinal surgeries and related studies showing benefits followed. (9)(10). Wang et al. presented the first published evidence for ERAS in craniotomy in 2019, with 140 patients undergoing surgery for both supra and infratentorial tumors. (11) In a series of publications that followed closely, registered under the same trial number, this group reported improved benefits in glucose homeostasis, (12) patient satisfaction(13) and a decreased incidence of postoperative nausea and vomiting (PONV) among those having infratentorial tumor resection (14) as benefits of their ERAS protocol. To the best of our knowledge, we are the first group, from outside of China, to report the implementation and benefits of ERAS protocol in craniotomy patients.

ERAS protocols are flexible and adapted to individual centers, keeping the basic tenets in place. This is well demonstrated when the two protocols (ours and Wang et al.) are compared. Many components were based on previous recommendations and were similar between our groups (4)

The differences are as follows-

Pre-operative phase-In our center, relatives are allowed a significant role in patient mobilization, feeding, and patient care - ignorance, fear, and hesitation among them delays ambulation, nutritional intake, and rehabilitation during and after the hospital stay. Our pre-operative counseling involved an in-depth of education of the relatives, including empowering them to question delays in feeding or ambulation orders and removal of foley's catheter, if any. We educated them on the harmful effects of smoking and alcohol, but abstinence was not essential. As our surgeries were restricted to supratentorial tumors, no added focus than the conventional existed for PONV risk stratification.

We administered maltodextrin (a complex carbohydrate- Proencecarbogain, 100mg = 380 Kcal) drink in different dosages, volumes and times - 200ml (100mg) the night before and 100 ml (50 ml) just 2 hrs before surgery vs. Wang’s 400 ml maltodextrose fructose solution on the morning of the day of surgery.

We had a more aggressive analgesia plan in Gr E in the form of flupiritine perioperatively (no preemptive analgesia by Wang et al.) and bilateral complete scalp blocks along with skin site infiltration (as opposed to only incision site infiltration by Wang et al.). This enabled us to have a stricter postoperative VAS guided pain management plan- NSAIDS up to a VAS of 4 and Inj Fentanyl beyond VAS 4. Unlike Wang et al., we did not emphasize on a difference in the ways of stitching/ craniotomy closure or type of suture used between the two groups.

The routine protocols such as antimicrobial preparation, shaving policies, respiratory interventions, goal-directed therapy, and temperature control were the same between Wang et al. and us.
We found a significant reduction in the proportion of patients requiring an ICU stay of > 48 hours, although there was no significant difference in the total duration of hospital stay. Ours is a public hospital with highly subsidized charges for patient care: most patients are poor and travel far, with limited post-discharge care. The factors affecting the length of postoperative hospital stay are known to vary widely. (15) Our focus was on an early discharge from the ICU/HDU area, which is in high demand (free to the patients). Therefore, recognizing that some patients may have a more prolonged ICU stay due to postoperative complications, our primary outcome was pragmatic- reducing the proportion of patients who stayed for > 48 hrs by 50%. (16)

The patients in the ERAS group had significantly lower insulin requirements than the controls over 48 hrs to achieve similar blood glucose targets. The practice points for instituting a protocol for and the benefits of pre-operative carbohydrate loading are nicely summed by Sarin et al. in 2017. (17) Without having measured serum insulin levels (12), we have demonstrated a reduced stress response and improved postoperative glucose control requiring a lower dose of postoperative insulin.

Scalp blocks provide better attenuation of inflammatory and hemodynamic response to craniotomy and better postoperative analgesia than incision site infiltration with local anesthetics (LA). (18) This, along with the addition of flupiritine, a centrally-acting nonopioid analgesic, with selective action on neuronal potassium channels (Kv7), resulted in significantly improved post-surgical VAS cored in GrE. Flupiritine has been used previously in patients undergoing craniotomy to reduce pain and anxiety perioperatively. (19–21) As compared to the study by Wang et al., we achieved more stringent goals (VAS<4) without opioids, and the dose of fentanyl required to manage episodes with VAS >4 was significantly less in the ERAS group.

The strengths of our study are the inexpensive interventions and the pragmatic reproducible endpoints. ‘Availability’ of family members to care for their patients is common in low, middle-income countries (LMIC) where cultural values and norms encourage family involvement. Many systems utilize this to their strength. (22)(23), and we used this concept to ensure adherence to the protocol at all stages, minimizing dropouts.

The lack of randomization is a definite limitation of our study. In 2017, ERAS protocols were allowed to be randomized in gastrointestinal oncosurgeries by our institute ethics committee; evidence in craniotomy patients was inadequate to allow randomization, and patients were to be allowed to chose their treatment arm after full disclosure. Our experience was, that initially getting families and patients to consent to be a part of the study (GrE) was tricky, but by the first ten patients, word had spread regarding the ‘early’ return of patients to the ward after surgery- then on, getting consent was easier and we made all attempts to keep the two arms equal by allocating consenting patients sequentially to either group. Even so, selection bias cannot be ruled out completely. As for most clinical research involving surgeries, blinding the patient, surgical or anesthetic teams was not possible. During the study we felt that the extra attention given to the GrE during pre-operative counseling and the empowerment of the relatives might have contributed to a greater willingness and even request for an early discharge from the ICU/ HDU: this effect can only be
considered desirable, and not a deterrent to the validity of the protocol. The generalisability of our primary result may depend on institute protocols for ICU discharge. We believe that they will be replicable in centres with limited ICU resources (specially if public funded) in other parts of the world. The secondary outcomes were based on internationally accepted protocols, and therefore will have external validity.

**Conclusion**

In this study, we have adapted the ERAS protocol to a neurosurgical setting, showing its feasibility and benefits in terms of early discharge from the ICU/ HDU along with better pain and blood sugar control postoperatively. ERAS protocols are bundles of care and include various interventions, and further studies are needed to standardize these for the patients undergoing craniotomy such that they may be kept pragmatic and easy to implement.

**Abbreviations**

ERAS (Enhanced Recovery After Surgery)

ICU (Intensive Care Unit)

HDU (High Dependency Unit)

IEC (Institute Ethics Committee)

CTRI (Clinical Trials Registry of India)

ASA (American Society of Anesthesiologists)

SPSS (Statistical Product and Service Solutions)

CT (Computed Tomography)

VAS (Visual Analogue Scale)

NSAID (Non-Steroidal Anti-inflammatory Drugs)

PONV (Post-Operative Nausea and Vomiting)

LA (Local Anesthetics)

LMIC (Low, Middle – Income Countries)

**Declarations**

**Ethics approval and consent to participate**
We confirm adherence to ethical guidelines, indicate ethical approvals, and the use of written informed consent for each patient included in the study. The institute Ethics Committee (IEC) is that of All India Institute of Medical Sciences Bhubaneswar, and the approval number IEC/AIIMS BBSR/PG T/2017-18/18.

**Consent for publication**

Not Applicable

**Availability of data and materials**

The original data and materials are with the corresponding author and can be obtained on reasonable request.

**Competing interests**

The authors declare no conflicts / competing of interest.

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None of the authors have received any funding for this project.

**Authors contribution**

Project conceptualization – ST, AE, SSJ, SN

Study design – ST, AE, SSJ, SN, RNS

Conduct of study – ST, AE, SSJ, SN, RNS

Statistical analysis – ST, AE

Manuscript design – AE, SSJ, ST, RNS, SN

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under consideration by another journal. Inclusion of the Conflict of Interest statement for all authors is confirmed. A reporting check-list is confirmed.

**TRIAL REGISTRATION**

Clinical Trial Registry of India (CTRI/2018/04/013247)

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