Preoperative steroid for enhancing patients’ recovery after head and neck cancer surgery with free tissue transfer reconstruction: protocol for a phase III, placebo-controlled, randomised, double-blind study (J-SUPPORT 2022, PreSte-HN Study)

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ABSTRACT

Introduction There is no established methodology for the perioperative management of head and neck cancer surgery and free tissue transfer reconstruction (HNS-FTR). A single dose of corticosteroid administered immediately before surgery has been shown to reduce postoperative pain and nausea/vomiting after some types of surgery. However, the efficacy of this strategy has not been demonstrated in HNS-FTR, and the increased risk of infectious complications associated with its use cannot be ruled out. This phase III, placebo-controlled, randomised, double-blind, comparative, multicentre study seeks to determine if preoperative administration of corticosteroid hormone has an adjunctive effect in terms of reducing pain and nausea/vomiting after surgery and improving the quality of postoperative recovery.

Methods and analysis Using the minimisation method, patients undergoing HNS-FTR are currently being recruited and randomly assigned to a study arm at a 1:1 allocation rate. The study treatment arm consists of 8.0 mg of dexamethasone phosphate dissolved in 100 mL of saline administered as a single dose by intravenous infusion. These treatments will be administered in a double-blind fashion. All patients will receive perioperative care according to the common multicentre enhanced recovery after surgery programme. The primary endpoint is the quality of postoperative recovery, as determined by the area under the curve (AUC) for total score on the Japanese version of the Quality of Recovery Score (QOR-40J) on postoperative days 2 and 4. The point estimate and CI for the difference in the AUC between the groups on postoperative days 2 and 4 will be calculated.

Ethics and dissemination The study will be performed in accordance with the Declaration of Helsinki and Japan’s Clinical Trials Act. The study protocol was approved by the Certified Review Board of National Cancer Center Hospital East (Reference K2021004).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first multicentre, placebo-controlled, double-blind, randomised trial to evaluate the efficacy of preoperative corticosteroid hormone administration immediately before surgery in head and neck cancer surgery with free tissue transfer reconstruction.

⇒ The primary endpoint is a patient-reported outcome that directly reflects the patients’ quality of postoperative recovery.

⇒ If the results of this study prove our hypothesis, it is expected to make a significant contribution to enhancing the postoperative recovery of patients undergoing head and neck cancer surgery with free tissue transfer reconstruction.

⇒ The limitation is that the study does not assess a completely homogeneous population, since the surgical procedures included in the study encompass a variety of surgeries.

Trial registration number The study was registered in the Japan Registry of Clinical Trials (jRCTs031210593; V3.0, November 2021, available at https://jrcr.niph.go.jp/en-latest-detail/jRCTs031210593).

INTRODUCTION

There is a need to develop minimally invasive surgical techniques and improve perioperative management to overcome the invasiveness of surgery, promote postoperative recovery and improve the quality of recovery. Originally introduced as a bundle for perioperative management in patients with colorectal cancer, the enhanced recovery after surgery
(ERAS) programme combines several evidence-based methods for perioperative management. A multicentre study found that perioperative management of colorectal cancer according to the ERAS programme reduced postoperative hospital stay from 6–10 days to 2–3 days. Today, the ERAS programme has evolved and is being used as a perioperative support measure in various conditions, especially in the surgical treatment of cancer.

In surgery for head and neck malignancies, defects associated with resection are often reconstructed structurally and functionally by free tissue transfer reconstruction. Head and neck cancer surgery with free tissue transfer reconstruction (HNS-FTR) is a relatively invasive procedure because of the multiple surgical fields involved and the long operation time. Some institutions have already been practicing ERAS for HNS-FTR. In addition, a meta-analysis has shown that the length of hospital stay decreased in the ERAS group for these surgical procedures. However, it is unclear whether the suffering of patients due to HNS-FTR has been actually alleviated, and thus further investigation and improvement of the ERAS programme are required.

We previously conducted a longitudinal study of 57 patients who underwent HNS-FTR from 2017 to 2018 whose perioperative management was conducted in accordance with the ERAS programme and included a single preoperative dose of dexamethasone. Early mobilisation and early enteral nutrition were implemented and postoperative pain was well controlled. We compared outcomes related to inflammatory markers and body fluid balance in this ERAS dexamethasone group with those in 102 historical controls who underwent HNS-FTR before we started implementing preoperative dexamethasone. Early mobilisation and early enteral nutrition were implemented and postoperative pain was well controlled. We compared outcomes related to inflammatory markers and body fluid balance in this ERAS dexamethasone group with those in 102 historical controls who underwent HNS-FTR before we started implementing preoperative dexamethasone and found that the inflammatory marker levels were significantly lower in the ERAS dexamethasone group. Furthermore, there were significant reductions in hypotensive events and excessive postoperative weight gain in this group, indicating significant improvement in their postoperative fluid balance.

A single preoperative dose of corticosteroid hormone has been shown to reduce postoperative pain and decrease the use of opioids. A meta-analysis of 24 randomised controlled trials that included 2751 patients compared the effects of preoperative administration of the corticosteroid hormone dexamethasone versus placebo on postoperative pain using a variable-effects model. The results showed that dexamethasone administered immediately before surgery is effective in reducing postoperative nausea/vomiting. HNS-FTR is a long operation with a high risk of postoperative nausea/vomiting. Given that postoperative vomiting increases the risks of wound dehiscence, wound infection and pneumonia, its prevention is an important issue.

In patients undergoing surgery for cancer of the oesophagus, an adjacent organ in the head and neck region, a single dose of corticosteroid hormone administered before surgery was reported to reduce surgical invasiveness and promote postoperative recovery. Similarly, a double-blind, randomised controlled trial in patients undergoing thyroidectomy reported that a single preoperative dose of corticosteroid hormone suppressed postoperative nausea/vomiting, decreased postoperative pain and improved postoperative voice function. However, the effects of preoperative corticosteroid hormone administration have not yet been established in patients with head and neck cancer. A clinical trial in patients undergoing HNS-FTR (ie, the same participants as in the present study) found that a significantly increased incidence of postoperative infection in patients who received corticosteroid hormone. That study used dexamethasone, which was administered three times on the day of surgery, twice on postoperative day 1 and once on postoperative day 2, for a total dose of 60 mg. We attribute the negative outcome in that study to administration of an excessive amount of dexamethasone. However, HNS-FTR is not a clean surgical procedure, and the possibility of negative effects such as the increased risk of postoperative infection, cannot be ruled out. Therefore, it is worthwhile to examine the usefulness of a single dose of corticosteroid hormone administered immediately before HNS-FTR.

Objective and study design

This multicentre, phase III, placebo-controlled, randomised, double-blind trial is being conducted to determine if preoperative administration of the steroid hormone dexamethasone has an adjunctive effect in reducing postoperative pain and nausea/vomiting and improving the quality of recovery in patients undergoing HNS-FTR who receive perioperative ERAS management.

METHODS AND ANALYSIS

This study protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline and SPIRIT-PRO Extension.

Eligible patients must be 20 years of age or older, be scheduled for HNS-FTR, have provided written informed consent, have no history of radiation therapy, not be receiving regular insulin and not be regular corticosteroid users. Details of the study eligibility criteria are shown in box 1.

Patient and public involvement

The patients and/or the public have no involvement in the design, conduct, reporting, or dissemination plan related to this research.
**Box 1 Eligibility criteria**

**Inclusion criteria**
1. At least 20 years of age.
2. Scheduled to undergo surgery for head and neck cancer, including resection of the primary tumour and reconstruction using free tissue transfer.
3. Written informed consent obtained.
4. Eastern Cooperative Oncology Group performance status 0–2.

**Exclusion criteria**
1. History of hypersensitivity to dexamethasone.
2. Current treatment with any of the following agents: disulfiram, cyanamide, desmopressin acetate hydrate, rilpirivir hydrochloride, rilpirivir hydrochloride/tenofovir, alafenamide fumarate/emtricitabine, rilpirivir hydrochloride/tenofovir disoproxil fumarate/emtricitabine, rilpirivir hydrochloride/dolutegravir sodium, dactactasvir hydrochloride, asunaprevir, daclatasvir hydrochloride/asunaprevir/beclabuvir hydrochloride.
3. Active infectious disease, such as tuberculosis, viral illness or mycosis.
4. Active thrombosis.
5. Poorly controlled diabetes requiring regular insulin use.
6. Psychiatric illness or psychiatric symptoms that interfere with daily life.
7. Active digestive ulcer.
8. Poorly controlled glaucoma.
9. Continuous preoperative use of oral corticosteroid or other immunosuppressive agent for autoimmune disease.
10. History of radiation therapy to the head and neck region.
11. Conditions such as cognitive impairment, total blindness or orthographic blindness that could make it difficult for the patient to complete the QoR-40J questionnaire or use the visual analogue scale (VAS).
12. Significant impairment of physical activity before surgery, such as stroke-related paralysis.

**Recruitment**
The participants are being recruited at the National Cancer Center Hospital, National Cancer Center Hospital East and Miyagi Cancer Center in Japan.

**Randomisation**
On enrolment and after providing informed consent, patients are randomly allocated to the study treatment arm or standard treatment (placebo) arm using an electronic data capture (EDC) system. Patients are randomised in a 1:1 allocation ratio using the minimisation method with adjustment for study site and operative procedure (laryngectomy, reconstruction using a free fibula flap, or other method) (figure 1).

There was agreement among the researchers that there should be two allocation factors for institutions and operative procedures in this study, based on the sample size. HNS-FTR is an operation involving a variety of procedures. Laryngectomy and fibula reconstructive surgery were employed as an allocation factor based on the operative procedures because they directly impair patients’ quality of recovery due to speech loss and the influence on walking and thereby affect the QoR-40J score, which is the endpoint of this study.

**Intervention**
The study treatment arm consists of 8.0 mg of dexamethasone phosphate (dexamethasone 6.6 mg) dissolved in saline and administered as a single dose by intravenous infusion 30–60 min before the start of surgery. The standard treatment (placebo) arm consists of the same amount of saline administered by intravenous infusion. Both trial preparations will be administered in a double-blind fashion. All participants will receive perioperative care according to the ERAS programme, including early mobilisation, nutritional support, early enteral nutrition, and management of pain and nausea/vomiting.

Multimodal pain management by ERAS will be implemented through regular administration of oral acetaminophen 2000 mg/day and intravenous fentanyl starting the day after surgery. When a patient has pain, a bolus dose of flurbiprofen axetil intravenous, acetaminophen intravenous or fentanyl can be used. To promote gastrointestinal motility, magnesium oxide will be regularly administered starting the day after surgery, and intravenous metoclopramide or prochlorperazine will be administered at the onset of postoperative nausea/vomiting.

Patients will be withdrawn from the study if their surgery is cancelled or not performed, if they no longer wish to participate, or if they die.

**Masking**
Patients and their attending clinicians are blinded to treatment assignment. Treatment allocation is known only to a non-blinded pharmacist with no involvement in patient care at each participating site. If necessary for treatment purposes in a specific case, the pharmacist can use the key open method to unblind the data.

**Assessment of endpoints and outcome**
The primary endpoint of the study is the quality of postoperative recovery, determined by the area under the curve (AUC) for the total score on the Japanese version of the Quality of Recovery (QoR-40J) score on postoperative days 2 and 4. Healthcare providers will collect QoR-40J scores with no monitoring. Key secondary endpoints are postoperative pain and postoperative nausea/vomiting. Study investigators will perform the evaluations by using a visual analogue scale (VAS) preoperatively and on postoperative days 1–5 and 7. The recall time for symptoms will be 24 hours. Other endpoints and the assessment schedule are shown in box 2 and online supplemental table 1, respectively. All evaluations will be completed during the hospitalisation period.

The protocol treatment is a single dose of corticosteroid hormone or placebo plus perioperative support provided through the ERAS programme, extrapolated from the perioperative support already provided in routine practice at all participating centres. No situation in which the intervention would need to be discontinued is envisaged.
Assessment of quality of postoperative recovery

The QOR-40\textsuperscript{27} is a questionnaire for assessing the quality of recovery of postoperative patients, and this study will use the Japanese version (QoR-40J),\textsuperscript{27,28} for which the validity of the translation has been confirmed. This questionnaire contains 40 items measuring five dimensions: physical comfort (12 items), emotional state (9 items), physical independence (5 items), psychological support (7 items) and pain (7 items). All questions pertain to the 24 hours period before answering the questionnaire.

The QoR-40 has been used in several previous studies in other areas to investigate the quality of postoperative recovery and patient satisfaction with preoperative administration of steroid hormone.\textsuperscript{29–32} In this study, we will use the QoR-40J score to assess the primary endpoint of the quality of postoperative recovery in patients who receive perioperative management as part of the ERAS programme.

The observation schedule is shown in online supplemental table 1. The AUC values for the mean QoR-40J scores on postoperative days 2 and 4 will be compared between the two arms as the primary endpoint. Preoperative and postoperative pain and nausea will be assessed using a VAS.

In our preceding study in which the quality of recovery after surgery in HNS-FTR was examined using QOR-40J,\textsuperscript{15} a marked decrease in the QOR-40J score was observed at the early stage of postoperative day 3. In contrast, on postoperative day 7, the recovery was comparable to that seen before surgery. Therefore, we concluded that it is important to improve the quality of recovery in the early postoperative period. The AUC values on postoperative days 2 and 4 were set as the primary endpoints for this study because the quality of recovery on these days was deemed important. In addition, our preliminary study verified that the QOR-40J questionnaire can be administered on postoperative day 2 with almost no missing data.\textsuperscript{33}

Data collection methods

The investigators at each study site will maintain individual records for each patient as source data, including medical records, laboratory data, a patient diary, a copy of the informed consent form and other records or notes. The J-SUPPORT Data Center at the National Cancer Center Hospital will collect all study data. Enrolment, randomisation data collection and monitoring will be performed using the Viedoc 4 and Viedoc Me EDC system.

Figure 1  Diagram showing the flow of patients through the study. ERAS, enhanced recovery after surgery; PRO, patient-reported outcome.
Box 2  Study endpoints

<table>
<thead>
<tr>
<th>Primary endpoint</th>
</tr>
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<tr>
<td>⇒ Quality of postoperative recovery (AUC for the QoR-40J total score on postoperative days 2 and 4).</td>
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<table>
<thead>
<tr>
<th>Key secondary endpoints</th>
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<tr>
<td>⇒ Postoperative pain (AUC for the VAS score on postoperative days 1, 2 and 3).</td>
</tr>
<tr>
<td>⇒ Postoperative nausea/vomiting (AUC for the VAS score on postoperative days 1, 2 and 3).</td>
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</table>

<table>
<thead>
<tr>
<th>Other secondary endpoints</th>
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<tr>
<td>⇒ QoR-40J composite score on postoperative days 2, 4 and 7.</td>
</tr>
<tr>
<td>⇒ Comfort, physical capacity, patient support, pain and emotion scores on the QoR-40J on postoperative days 2, 4 and 7.</td>
</tr>
<tr>
<td>⇒ Postoperative length of hospital stay.</td>
</tr>
<tr>
<td>⇒ Time to completion of postoperative discharge criteria.</td>
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<tr>
<td>⇒ Severity of postoperative pain (VAS score, postoperative fentanyl requirement, use of analgesic rescue).</td>
</tr>
<tr>
<td>⇒ Postoperative nausea/vomiting (VAS score, use of antiemetic rescue medication).</td>
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<tr>
<td>⇒ Duration of enteral feeding.</td>
</tr>
<tr>
<td>⇒ Whether or not enteral feedings were interrupted.</td>
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<tr>
<td>⇒ Time of mobilisation.</td>
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<tr>
<td>⇒ Perioperative complications of Clavien-Dindo classification grade II or higher (e.g., wound infection, wound dehiscence, leakage, skin necrosis, reconstructed flap necrosis, pneumonia, sepsis, supraventricular arrhythmia, bradycardia, ischaemic heart disease, heart failure, deep-vein thrombosis, cerebral infarction, obstructive ileus, pleural effusion, chylothorax, lymphorrhoea, salivary fistula, postoperative bleeding).</td>
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<tr>
<td>⇒ Inflammatory response to surgical invasion (interleukin-6, C reactive protein, albumin, neutrophils, lymphocytes, neutrophil–lymphocyte ratio, maximum body temperature).</td>
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<td>⇒ Fluid balance (change in body weight, presence of hypotension).</td>
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<tr>
<td>⇒ Blood glucose control.</td>
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<td>⇒ Occurrence of delirium.</td>
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The analysis set in this study is defined as the set of subjects who underwent randomised allocation, excluding those who did not undergo surgery. We estimated that about 2% of cases will not undergo surgery. However, considering the fact that there will be a certain percentage of cases in which the primary endpoint (ie, the QoR-40J score) cannot be described, we estimated that the percentage of cases in which the primary endpoint can actually be analysed is about 85%. Therefore, we considered that 76 cases (ie, 1.2 times the aforementioned 64 cases) were necessary. Furthermore, allowing for ineligible cases, we set the required number of patients at 90 per group, or 180 in the two groups.

**Statistical analysis**

We will use all QoR-40J total scores for each time point (ie, on postoperative days 2, 4 and 7). General linear models that include group, time point, time-by-group interaction and the baseline QoR-40J score as explanatory variables will be used to summarise the longitudinal change in QoR-40J score. An unstructured covariance matrix is assumed, and robust standard errors will be calculated for parameter estimates using the maximum likelihood method and considering missing QoR-40J scores. The point estimate and CI will be calculated for the difference in the AUC values on postoperative days 2 and 4 between the groups. No interim analysis will be performed.

**Data monitoring**

The J-SUPPORT data centre will oversee the conduct of the study and data collection process. The clinical data managers will compile central data monitoring reports twice a year and report to the principal investigator and site investigators. An Independent Data Monitoring Committee that has been established will review the safety data if serious adverse events occur.

**Reporting of adverse events**

Study investigators at each site will report serious adverse events to an Approved Clinical Research Review Committee. Adverse events are defined as undesirable or unexpected illness or symptoms with a severity of Clavien-Dindo grade III or higher occurring in patients while hospitalised and receiving treatment during the study period. Reports will be filed for deaths, serious adverse events that may lead to death, serious adverse events that require hospitalisation or prolonged hospitalisation at a medical institution for treatment, and serious adverse events that may lead to disability or impairment.

**Auditing**

The auditor will conduct on-site audits at the participating sites to ensure the reliability of the materials used and the information collected through clinical research, from the perspective of ensuring reliability in clinical research and protecting the participants in this clinical research.

(Viedoc Technologies, Uppsala, Sweden). Investigators at each site will enter data into the electronic case report form using the EDC system. Patients will use an electronic tablet device to provide patient-reported outcome data or use a paper questionnaire when they are not able to use an electronic device.

**Sample size calculation**

The clinical hypothesis of this study is that preoperative administration of dexamethasone for resection of head and neck malignancies and free tissue transfer reconstruction improves patient satisfaction and contributes to accelerated postoperative recovery. The minimal clinically important difference for the QoR-40 is reported to be 6.3. We reviewed the results of previous studies and estimated that the mean difference in the AUC between the placebo and dexamethasone groups on postoperative days 2 and 4 would be 10. If the difference between the groups is set at 10 and the SD is set at 20 with a two-sided significance level of 5% and a power of 80%, the number of patients required would be 64 per group with 1:1 allocation.
Protocol amendments
The Certified Review Board (CRB) will review requests for modification and modifications to the study protocol. The CRB will revise the informed consent materials to be given to participants and adapt them to accord with guidelines.

ETHICS AND DISSEMINATION
The study will be performed in accordance with the Declaration of Helsinki and Japan’s Clinical Trials Act. The protocol was reviewed by the Scientific Advisory Board of the Japan Supportive, Palliative and Psychosocial Oncology Group (J-SUPPORT) and approved as a J-SUPPORT 2022 study. The study was approved by the Certified Review Board National Cancer Center Hospital East (reference: K2021004) and is registered in the Japan Registry of Clinical Trials (jRCTs031210593, https://jrcr

Confidentiality
Personal information, such as name, address, and medical ID, will be not collected.

Access to data
Only clinical data managers at the central data centre have access to the case data reported via the EDC system.

Dissemination policy
The results of this study will be submitted for publication in an international peer-reviewed journal and the key findings will be presented at international scientific conferences. Authorship will be ascribed in accordance with International Committee of Medical Journal Editors guidance.

Availability of data
The datasets will be available from the corresponding author on reasonable request.

DISSUSSION
A single dose of corticosteroid hormone administered before HNS-FTR is expected to reduce postoperative pain, postoperative nausea/vomiting and invasive adverse events after surgery and to have a positive impact on the quality of postoperative recovery. If the efficacy of a single dose of corticosteroid hormone administered immediately before surgery is confirmed, considerable suffering could be alleviated in patients undergoing highly invasive treatment for head and neck cancer. The findings of this trial will determine whether our ERAS programme can be introduced nationwide in the future.

Trial status
The study is ongoing, with patients currently being enrolled. Recruitment started in February 2022. At the time of submission of this protocol for publication (October 2022), 33% of the target number of patients have been recruited. We thus expect to complete recruitment by October 2024.

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Contributors
The study was conceived by TS, TI, KK, SY and KM and designed by SZ, TY and TMiyaji. TS, TI, SY, KE and KM wrote the main text of the manuscript and TO compiled a double-blind randomisation manual. TMashiko and MK set up the EDC system used in the trial. All authors read and approved the final manuscript.

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Competing interests
None declared.

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Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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Not applicable.

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Supplemental material
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