Boston Children's Hospital

Continuous Erector Spinae Block versus Continuous Paravertebral Block Following Thoracotomy: A Randomized, Controlled Non-Inferiority Study

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NCT#: NCT03768440

Version Date: 05/09/2022

TITLE:

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A. Specific Aims/Objectives:

Overall Aim: To evaluate the efficacy of continuous erector spinae block (ESB) versus continuous paravertebral block (PVB) for postoperative analgesia in children and adolescents undergoing surgical procedures via unilateral thoracotomy.

Hypothesis: The investigators hypothesize that ESP block efficacy is not inferior to that of PVB with respect to pain control and consumed opiate equivalents at 24, 48 and 72 hours postoperatively.

We propose to evaluate the comparative efficacy of the continuous erector spinae block (ESB) versus continuous paravertebral block (PVB) for patients undergoing unilateral thoracotomy by means of a randomized, controlled non-inferiority study (based on a threshold of clinical significance being defined as a 15% difference) comparing rescue analgesic requirements, rendered as opiate equivalents, at 24, 48 and 72 hours postoperatively. Secondary measures will include pain scores, adverse events, time to perform the block in the operating room, time to discharge from the ICU, time to extubation and patient disposition after surgery.

B. Background and Significance:

Regional anesthesia—and pediatric regional anesthesia in particular—is a rapidly evolving subfield of anesthesia practice driven with considerable urgency by the growing recognition that even appropriate perioperative narcotic administration can have significant derogatory long-term effects.

Regional anesthetics can provide targeted, continuous analgesia to select dermatomes with minimal additional patient risk and have become routine components of opioid-sparing intraoperative and postoperative pain management plans for surgical patients at BCH. In addition to the postulated benefit of reducing overall opioid exposure and potentially reducing the risk for long term physiologic and behavioral dependence upon opioids, regional anesthetics may allow for earlier extubation after selected surgeries, shorter ICU, PACU and inpatient admissions, earlier mobilization, fewer gastrointestinal complications, and improved patient satisfaction scores.

Given the rapid evolution of the field of regional anesthesia and the fact that there are often multiple approaches for achieving analgesia in a select set of dermatomes, there are often a variety of regional anesthetic options for any given surgery. Some approaches are longstanding and well-studied, but with increasing frequency since the advent of ultrasound guidance, newer, novel nerve block options exist. As it is often expensive and work-intensive to thoroughly evaluate a given regional technique

with a controlled pediatric trial, many of these blocks become standards of practice based on anecdote, retrospective analysis, or simply belief in the putative benefits of regional anesthetics.

We are fortunate at BCH to have one of the largest concentrated pediatric surgical populations in the US. We also have an active, and well organized regional anesthesia service. Because of this, we are in a unique position to more thoroughly evaluate the effectiveness and safety of regional anesthesia in children. Furthermore we feel it is critical that institutions such as BCH take a leading role in documenting the effects of regional anesthesia on the most important outcome measures when considering perioperative medicine. These include: overall pain management, surgical healing, functional recovery, long term pain symptoms, and emotional/behavioral outcomes after surgery.

Recently the ESB has become popular for providing analgesia after a number of anterior chest and abdominal procedures.[1-4] This is a simple interfascial plane block that can reliably provide unilateral chest and/or abdominal wall analgesia.[5] It has been described in numerous case reports and one case series as an effective block for management of unilateral thoracotomies, unilateral rib fractures, unilateral abdominal incisions and (when used bilaterally) for management of post-sternotomy pain.[6,7]

As an interfascial plane block in a compressible anatomical space, the ESB is thought to be safe in anticoagulated (or recently anticoagulated) patients.[8] It is fast becoming a preferred anesthetic option for these patients as opposed to neuraxial (e.g. epidural) and paraneuraxial blocks (i.e. paravertebral) nerve blocks.

Given the ESB's potentially favorable risk profile versus the other blocks (it is technically less challenging, more distant from critical structures, and thought to be safe in anticoagulated patients) it could provide both a safer and easier to perform regional anesthesia option for many patients.[6] It also offers a new option for a subset of anticoagulated patients for whom other regional techniques (epidural, paravertebral) are contraindicated.

Indeed, given the current information available related to the ESB, the regional anesthesia service at BCH has begun employing it when possible in circumstances where a PVB would commonly be used but is relatively or absolutely contraindicated. Patients undergoing thoracotomies while anticoagulated for cardiopulmonary bypass, aortic clamping, etc. have been successfully managed with continuous ESBs.[9] In addition, thoracotomies in patients with acquired (e.g. dilutional) and other pathologic coagulopathies have been managed with ESBs. As such, the ESB has been adopted for routine use in specific patient populations at BCH and has even occasionally been utilized in lieu of the more longstanding routine PVBs or epidural blocks for patients without contraindication for such.

Retrospective review of BCH outcomes data for 47 ESBs done for a variety of surgeries and populations has not revealed any significant differences between PVBs and ESBs in terms of adverse events, postoperative opiate use, median pain scores, or other standard outcomes measures. As this data is observational in nature, it is

difficult to draw firm conclusions as to the comparative efficacy of the two blocks. However, since there are differences in technical difficulty, relative contraindications, and there exist populations that might benefit from these blocks, it would be prudent to comparatively evaluate these blocks in a controlled, randomized, trial.

We propose to evaluate the comparative efficacy of ESBs and PVBs for patients undergoing unilateral non-cardiac thoracotomy by means of a randomized, controlled non-inferiority study (based on a threshold of clinical significance being defined as a 15% difference) comparing rescue analgesic requirements, rendered as opiate equivalents, at 24, 48 and 72 hours postoperatively. Rescue opiates will be available as needed by means of standard PCA/NCA demand protocols. Secondary measures will include pain scores, adverse events, time to discharge from the ICU, time to extubation, patient disposition after surgery, and time to perform the block in the operating room.

C. Preliminary Studies

While the PVB and, increasingly, the ESB are commonly used for postoperative management of numerous thoracic procedures in adults and children, there is little prospective data available for the efficacy of the blocks and no prospective data at all that we are aware of comparing the two blocks.

Retrospective studies and case reports of varying quality exist and they suggest that both ESBs and PVBs are efficacious and low risk, but no retrospective comparative data exist. The ESB has been described as having utility in the adult perioperative environment for patients undergoing breast surgery[10], shoulder surgery[11], thoracotomy/thoracoscopic surgery[3,12], thoracic spinal surgery,[13] and ventral abdominal surgery[1]. Two case reports have also described its utility in treating patients with chronic pain in the thoracic dermatomes [14]. There is much less published evidence in children; however there are case reports and case series describing its use for patients undergoing thoracic and abdominal surgery[6,15-17].

Large retrospective analyses of multiple pediatric regional anesthesia registries do exist and consistently report a very favorable safety profile for the provision of regional anesthetics in the pediatric population. A recent (2015) consensus statement from the American and European Societies of regional anesthesia (ASRA and ESRA) reported the risk profile of administering regional anesthetics to anesthetized children, citing a risk of postoperative neurologic symptoms of 0.93/1000 cases (>90% of which resolve completely within 1 month) and a rate of local anesthetic systemic toxicity of 0.08/10000 cases.[18]

As noted above, analysis of the retrospective outcomes data for the 47 BCH patients treated with ESBs following unilateral thoracotomy does not reveal significant differences in common outcome measures including postoperative opioid consumption or pain scores as recorded by nurses in our inpatient units when

compared to PVBs. While the numbers at BCH are small, there is no evidence that either of these block types is associated with any greater risk than that demonstrated by aggregate data from the various pediatric regional anesthesia registries. Information currently available suggests that regional blockade, when performed properly, carries a very low risk of morbidity and mortality in appropriately selected infants and children.[19] Furthermore, we have found no evidence of increased adverse events present in the ESB patients when compared to the PVB patients in our local analysis.

D. Design and Methods

(1) Study Design

We propose a randomized, controlled, non-inferiority trial to compare the effectiveness of ESBs versus PVBs for patients undergoing unilateral non-cardiac thoracotomy. We will compare rescue analgesic requirements, rendered as opiate equivalents, at 24, 48 and 72 hours postoperatively as the primary endpoint. Children and adolescents aged 1 month - 12 years of age will be recruited from Boston Children's Hospital, beginning December, 2018.

(2) Patient Selection and Inclusion/Exclusion Criteria

Patients who meet the criteria below will be recruited from BCH:

Inclusion Criteria:

1. ASA I – III status, undergoing unilateral thoracotomy for either esophageal atresia related intrathoracic procedures or other non-cardiac general surgical intrathoracic procedures.
2. Patients meeting the above inclusion criteria as well as having additional surgical access for their intrathoracic procedure(s) gained via the neck (i.e. "neck dissection") may also be included.
3. Ages 1 month – 12 years (including infants who go to the NICU)

Exclusion Criteria:

1. Patients undergoing procedures including pleurodesis, pleural stripping, and decortication or other procedures with widely distributed pleural disruption.
2. Patients with known coagulopathies.
3. Patients with severe neurodevelopmental delays.
4. Patients with previous chronic pain syndromes.
5. Patients with a history of opioid treatment at any point in the 2 months prior to surgery.
6. Lack of parental consent and/or child assent.

(3) Description of Study Treatments or Exposures/Predictors

Participants will have their medical record reviewed following enrollment for demographic information including: gender, age, weight and height, procedure, surgeon, laterality, and current and historical medication use. Enrolled patients will be

randomized to receive either an ESB with catheter placement at the end of the surgical procedure or a PVB with catheter placement at the end of the surgical procedure (procedures described below). The randomization process will be determined by the research team and only the team placing the block will know what type of block and catheter a patient received.

The blocks have very similar insertion points and thus can be easily masked by a small, retractable flap which will render them indistinguishable to clinical care staff while still allowing for inspection by a member of the research team. All members of the enrolled patients' primary care teams (i.e. those making pain assessments and giving rescue narcotics per standard floor protocols) will be blinded as to the block and catheter types.

All blocks and catheters will be placed by a member of the BCH regional anesthesia team in a sterile fashion at the end of the surgical procedure, utilizing the existing surgical positioning, draping, and sterile field. With the exception of the anatomical localization of the needle tip, the procedures are identical and proceeds as follows:

- The surgical field is re-prepped with a chlorhexidine solution, and additional sterile drapes are applied to demarcate the block placement area.
- The anatomical site of interest is localized with ultrasound.
    - Erector spinae block: T4/5 transverse process is identified with the ultrasound transducer in a parasagittal orientation
    - Paravertebral block: The paravertebral space (bound medially by the bodies of the vertebrae, intervertebral discs, and intervertebral foraminae; anterolaterally by the parietal pleura and the innermost intercostal membrane; posteriorly by the transverse processes of the thoracic vertebrae, heads of the ribs, and the superior costotransverse ligament) laying between T4/5 is identified using the ultrasound transducer in a transverse orientation
- 18g Tuohy needle is advanced to target area under direct ultrasound visualization.
    - Erector spinae block: The needle tip is advanced until it contacts the transverse process, just below the erector spinae muscle complex.
    - Paravertebral block: The needle tip is advanced until it is seen passing under the transverse process, immediately superior to the pleura
- Normal saline is injected to confirm appropriate needle tip position.
    - Erector spinae block: The erector spinae muscle is visualized to be elevated up off of the transverse process with normal saline injection
    - Paravertebral block: The pleura is seen to deflect downward with normal saline injection
- With confirmation of appropriate needle tip position, the initial local anesthetic bolus is injected using a weight-based dosing protocol.

- Following the bolus injection, a catheter is threaded into the space occupied by the local anesthetic bolus.
- Catheter tip position is verified by one or more of the following: ultrasound visualization of the catheter tip, ultrasound visualization of instilled normal saline and/or ultrasound visualization of a small hyperechoic (i.e. bright on ultrasound) injection of air.
- With the catheter tip position identified, the catheter is tunneled to a cutaneous exit point approximately 2-3cm from the incision using a Crawford needle.
- The catheter is dressed in standard fashion with an adhesive catheter anchor, Dermabond, Mastisol, Tegaderm and tape.
- A displaceable opaque flap is positioned over the dressed catheter insertion site.
- A label indicating that the catheter is a nerve-block catheter with its date of placement is applied to the catheter.
- Catheter placement is complete.
- Postoperative infusion of local anesthetic (per weight based protocol) via the nerve block catheter is initiated, and modified as necessary, under the direction of the Acute Pain Treatment Service using their standard clinical protocols for continuous nerve block infusions. (Note: the infusion medication and protocol for both block/catheter types is identical.)
- Procedural notes:
    - Minor deviations from the above procedure (e.g. small changes in sequence, needle entrance locations, amount of catheter deployed, etc.) are possible as the anatomy, positioning, etc. of individual patients varies. This is anticipated and allowable so long as such modifications remain within what is currently considered standard of care for the placement of these blocks and what is done in a given case is considered the appropriate standard of clinical care for that patient by the clinical providers placing the block(s).

All patients will have access to rescue opiates as needed by means of the standard PCA/NCA demand protocols utilized at BCH. In addition, all patients will be followed by the Acute Pain Service at BCH, enabling access to additional assessment and opioid treatment as needed 24 hours a day, 7 days a week. Floor/ICU nursing personnel are encouraged to call the Acute Pain Service if they feel pain management is not adequate in any case – this will be reinforced for patients included in this trial. In addition, one of the primary investigators will be available for consultation 24 hours a day to the Acute Pain Service for any desired consultation on study patients.

E. Definition of Primary and Secondary Outcomes/Endpoints

Primary:

- Rescue analgesic consumption at 24 hours, rendered as total opiate equivalents

Secondary:

- Pain scores at 24, 48 and 72 hours measured by the numeric rating scale (NRS), Wong-Baker FACES scale or FLACC scale as appropriate. (All three scales render pain on a scale of 0-10 where 0 is the least pain and 10 is severe pain.)
- Time to perform the block in the operating room.
- Time to discharge from the ICU.
- Time to extubation.
- Patient disposition after surgery.
- Adverse events.

F. Data Collection Methods

All patients will be assigned a unique personal identifier that will not be linked to any patient identifying information. Data collected during the study in case report forms will be entered into the Internal REDCap database or automatically collected via the Regional Anesthesia Outcomes Database and uploaded to that same database (this would include pain scores and opiate and/or other medication use).

Each day of the study, the catheter will be assessed for following adverse events: Presence or absence of catheter dislodgement (catheter out or no longer in a clinically effective position), catheter occlusion, catheter leakage (presence of local anesthetic under occlusive dressing), skin irritation (presence of hyperemic cutaneous reaction not present at dressing placement), and catheter infection (presence of purulent material) by a member of the study team. Intubations status (including extubation time, where indicated), catheter boluses and catheter rate adjustments (if present) will be recorded.

Research information collected on paper (or other physical media) during the study will be stored in locked cabinets with access limited to the Principal Investigator and research personnel affiliated with the study. Information that has been generated as, or transferred to, electronic media will be kept on password protected, secured data servers. All health information is protected by HIPAA (Health Insurance Portability and Accountability Act) and all health records will be kept confidential. Patients' birthdate, name, and all other identifying information will be removed when analyzing and reporting the data. Any personal identifying information will be stored separately from the other information provided by or about the patient and no personal identifying information will be reported in any publications or presentations. Identifying information will be kept in a password protected, secure file with limited access by research personnel. Once data collection is complete, identifying information will be destroyed.

G. Data Management Methods

All relevant information retrieved from the electronic medical record, by the PI and/or a member of the research team will be translated into an electronic form. Data collected in paper case report forms will be entered into the Internal REDCapfor intake and checking, and will be protected by encryption and password. Only authorized users are permitted access to the data files, and daily server back-up activities are executed to ensure data safety. All data will be stored on a password-secured research computer, and all data entered into the computers will be password protected. Procedures to ensure accurate and reliable data collection will include well-designed data forms and training.

H. Study Timeline

We plan to enroll a total of 88 patients in the study (44 patients randomized to reach arm of the trial; power analysis below). We anticipate that it would take approximately 2 years to complete enrollment in this study.

I. Adverse Event Criteria and Reporting Procedures

Adverse or unanticipated events will be reported as required to the Boston Children's Hospital IRB by the PI according to institutional reporting requirements. An Adverse Event refers to any untoward medical occurrence whether or not it is considered intervention-related.

As noted above, analysis of the retrospective outcomes data for the 47 BCH patients treated with ESBs demonstrates no evidence that this block type is associated with any greater risk than that demonstrated by aggregate data from the various pediatric regional anesthesia registries. Information currently available suggests that regional blockade, when performed properly, carries a very low risk of morbidity and mortality in appropriately selected infants and children.[19] Given this and the fact that even were the subjects to opt out of the study they would receive one of these blocks anyway as a part of their standard postoperative pain management plan, this study places the subjects at minimal risk for adverse events compared to non-participants.

Nevertheless, as there exist little prospective outcomes data related to the ES block, we will implement a rigorous system to follow and report any adverse events, including interim analyses by a non-blinded statistician, as described below:

Adverse Event Monitoring and Interim Data Review:

Adverse outcomes will be carefully tracked for all patients enrolled in the study. Enrollment will be halted and the IRB informed by the PI if any of the following conditions are met:

- 1 of any of the following serious adverse events:
    - Patient death.

- Pneumothorax directly resulting from placement or removal of the block and catheter as evidenced by: 1- lung puncture during placement resulting in a moderate to large pneumothorax on the side affected performed within 8 hours, and/or the development of a new air leak in an existing chest tube collection system. 2- The development of a new moderate to large pneumothorax within 8 hours after removal of the ESB or PVB catheter.
- Hematoma at the site of the catheter/block—causing pain or any neurological symptoms for the patient.
- Persistent neurologic symptoms lasting more than 3 days after a single shot block or catheter is removed.
- Local anesthetic systemic toxicity (any symptoms leading to this diagnosis by a study team participant)

- >2 of any of the following minor/moderate adverse events in aggregate:
  - Persistent bleeding at the site of the catheter insertion or block placement.
  - Leakage of local anesthetic from the catheter insertion site that leads to discontinuation of the catheter infusion.
  - Redness or superficial infection of the catheter site or site of the block placement.
  - Skin irritation at the site of the catheter insertion or block placement that results in greater than 3 cm of induration or is associated with pain.

- If there is determined to be a >15% effect difference (as described in Part B. Section K.) between the intervention types in the any one or more of the primary and/or secondary outcomes following interval data analysis at select time points (after 22 participants have completed the study and then again after an additional 22 participants have completed the study).
  - One of the study team's statisticians will not be blinded
  - The non-blinded statistician will perform the interval analyses at the specified intervals.
  - The non-blinded statistician will present these interim results directly to the PI if any result meets the above reporting criteria. The PI will subsequently inform the IRB of the finding(s) as described below..

- If there is a significant difference detected on interval analysis, this will be reported directly to the IRB. The IRB will advise the study team as follows:
  - Whether or not the study team (with the exception of the non-blinded statistician) shall remain masked;
  - Whether or not the protocol requires modifications of the study protocol based upon the review of the safety data;
  - Whether or not the protocol requires suspension or early termination because of serious concerns about subjects' safety;

- Whether or not the protocol requires suspension or early termination because study objectives have been obtained according to the pre-established statistical guidelines.

If there is a pause for any of the above reasons, continuance of the protocol will be at the discretion of the IRB in consultation with the study team. No individual care data will be reported unless there is a serious adverse effect. Reports will be done in an aggregated way.

Special note regarding ropivacaine and chloroprocaine:

Ropivacaine and chloroprocaine use in PVB catheters is the standard for clinical management in this patient population at this institution. Both are routinely used at BCH for all nerve blocks and regional anesthetics (chloroprocaine is the institutional standard for patients under 6 months of age). Known potential adverse advents of this mode of delivery of this medication include hypersensitivity, allergic reaction, hypotension and cardiac arrhythmias if injected intravascularly. The presence of any of these will be assessed by the primary anesthesiologist intraoperatively and treated appropriately at the time of block placement and initial bolus and further assessed for such daily by members of the research team and Acute Pain Service. Any occurrence of a possible adverse event or events will be documented and reported to the DSMB, the IRB and the Department of Anesthesia Quality Assurance Physician as appropriate. In the event of a serious adverse event, it will be reported to the DSMB and IRB immediately and the study halted until a thorough investigation into the cause can be made.

The relative safety of ropivacaine and chloroprocaine for use in regional anesthesia is supported by the information contained the Pediatric Regional Anesthesia Network (PRAN) database. The PRAN is a consortium of major pediatric centers in North America that manages a prospective data registry on pediatric regional anesthesia. From their database, which at this time comprises more than 130,000 pediatric regional anesthetics from numerous major centers in the US and Canada, ropivacaine (for example) is documented to be used in greater than 85% of pediatric regional blocks with a safety profile at least equivalent to, if not better than, bupivacaine.[20]

Further, ropivacaine and chloroporciane are very well studied in pediatrics. There is an extensive body of prospective clinical trials and clinical outcomes studies on these agents' pharmacokinetics, safety and clinical outcomes from infancy through adolescence. Our prescribing practices at BCH in the Regional Anesthesia and Acute Pain Services are derived from that body of PK information and consensus recommendations.

We therefore regard ropivacaine and chloroprocaine as the established standards of care for pediatric regional anesthesia and have selected them for use in this study.

J. Quality Control Method

Data quality control will be assured through automated and manual methods. The study database enhances data quality through required entry fields for critical data and automatic flags for missing or out-of-range data. Efforts will be made to minimize data entry error by the development of a user-friendly database and all data entry will be double-checked with the source files. Data will be audited for accuracy by investigators after being entered into the database.

Further, as noted above, we plan an interim data safety review and analysis of the collected data after the initial 22 patients in order to identify any significant, unexpected deviations from the standard of care that should be addressed.

K. Data Analysis Plan

At the time of data analysis, datasets will be downloaded from the InForm database and merged into Statistical Analysis Systems 9.3 for purposes of analysis. Missing data will be accounted for when the data is coded into respective variables.

Descriptive statistics will be generated in order to summarize demographic characteristics of patients enrolled. Data will be tested for normality using the Shapiro-Wilk test. Data will be presented as total n (%), means and standard deviations (SD) if the distribution appears normal, or medians and range when not.

Assuming normality, t-tests will be conducted to investigate the differences between the two randomized groups (to compare total opioid equivalents, time required to place the block, time to extubation, and time to discharge, etc.). If data does not appear to be normal, Wilcoxon Rank Sum/Mann-Whitney tests will be used for group comparisons. Repeated measure analysis will be used to compare pain scores over time between groups and when compared to baseline values. Adverse events and complications (if any) associated with the blocks will be recorded and categorized. Fisher's exact test will be used to compare the proportion of patients who reported adverse events between the two groups. $P<0.05$ will be considered statistically significant.

L. Sample Size Considerations

In order to show that the treatment under consideration (ESB) is not inferior to the current active control (PVB), we set the acceptable non-inferiority margin at 15% (0.16mg/kg) of the total opioid consumption based on historical rescue opiate data in a similar cohort. Assuming an alpha of 5%, 80% power, and that the mean consumption of opioids between the two treatments is equal, we estimate that a total sample size of 88 patients undergoing thoracotomy (randomized 1:1, n=44 per group) is needed to demonstrate non-inferiority of the new treatment (ESB). The sample size calculations are based on an expected mean opiate consumption of 1.06mg/kg for each block and a pooled standard deviation of 0.3 mg/kg.[21,22]

M. Study Organization

Roland Brusseau, MD will serve as principal investigator. Patient screening, recruitment, enrollment, and data collection will be performed by a designated member of the research team.

N. Potential Benefits

There are no direct benefits to the patients partaking in the study. Currently no data exists to recommend one block over the other for post-thoracotomy management. The results of this study may allow the investigators to report the relative non-inferiority of the ESB compared to the PVB and thus optimize efficacy, increase safety, and possibly make a regional anesthetic option available to patients for whom other, established techniques have been contraindicated.

O. Privacy Provisions

Information will only be made available to individuals who are part of the research team. Any results from tests performed for research purposes will not be placed in the medical record. Medical information collected for this study will only become part of your child's medical record if the information is determined to be pertinent to the care your child receives at Children's Hospital Boston. Disclosure of personal information may occur only when required by law.

P. Confidentiality Provisions

All identifying information such as dates of birth, names, and medical record numbers will be removed from the study database. All patients will be assigned to an ID number that will not be linked to any patient identifying information. Data collected for research purposes will not be entered into patient's medical record. All data will be electronically secured in a password protected private folder. Only research investigators and personnel affiliated with the study will have access to patient information.

Every effort will be made by research staff to keep patient information confidential. To ensure patient confidentiality, all research data will be secured in locked filing cabinets in a locked office. Any publications that result from this study will not be linked with personal identifiable information that would disclose the identity of study subjects.

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