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A Prospective Randomized Placebo Controlled Trial of Erector Spinae Plane Catheters in Cardiac Surgery Patients

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Introduction

Regional anesthesia techniques including Erector Spinae Plane (ESP) blocks have potential to provide chest wall analgesia, but the level of evidence for the applicability of this technique remains low. The RACER (Regional Anesthesia for Cardiothoracic Enhanced Recovery) study was designed with placebo control, double blinding, and randomization, to determine if the use of lidocaine via ESP catheters changed postoperative opioid requirements, pain scores, inflammatory biomarkers, or other measures of recovery in patients undergoing sternotomy for elective cardiac surgery. Here we present the preliminary analysis of this trial.

Materials and Methods

Following institutional review board approval (protocol ID 47647) and registration on clinicaltrials.gov (NCT03781440), patients scheduled for elective coronary and/or valve (aortic or mitral) surgery were recruited between January 2020 and September 2021. Randomization by permuted blocks was performed and an investigational pharmacy prepared study infusions with identical labels for clinical use.

On the day of surgery, all participants received bilateral ultrasound guided thoracic ESP catheters in the preoperative area immediately prior to their procedure. Intraoperative monitors and anesthetic medications were at discretion of attending anesthesiologist with exceptions of fentanyl, ketamine and dexmedetomidine, for which the anesthesia team received a standardized protocol for all participants.

Prior to incision, patients received an ESP catheter bolus of study drug (0.25mL/kg up to 20mL per side – equivalent of lidocaine 0.5% 0.75mg/kg per side). At the completion of surgery, the ESP catheters were dosed via infusion pump with intermittent boluses every 2 hours in each catheter (volume equivalent to lidocaine 0.5% 0.5mg/kg) alternating hourly between sides. ESP infusions were continued until chest tube removal or POD5.

Blood samples for biomarker analysis were drawn preoperatively, immediately postoperatively, and 24 and 48h after surgery. Blood samples were processed per study protocol in heparinized tubes and centrifuged at 4 degrees C within 30 min of collection to extract plasma. The plasma samples were immediately aliquoted and stored at -80 degrees C until analysis. After study accrual was completed, all plasma samples were analyzed in duplicate by commercial assay using a multiplexed human inflammatory

cytokine panel assayed on a Bio-Plex 200. This panel included proinflammatory cytokines IL-6, IL-1b, TNFa, IFNy, and anti-inflammatory cytokine IL-10.

Patients received postoperative care per usual ICU and floor protocols including opioid analgesia at team and patient discretion, rapid extubation protocol, early mobilization, and invasive line management per team discretion. The primary outcome was postoperative opioid requirement. Secondary outcomes included pain scores, duration of mechanical ventilation, length of hospital and ICU stay, time to first bowel movement, and inflammatory biomarker profiles. Statistical analysis was completed in R and Excel (t-test for continuous variables and Fisher's exact test for categorical comparisons) according to group allocation as intention to treat.

Results/Case Report

Sixty patients were recruited and randomized, with 28 in the treatment arm and 32 in the control arm. No patient safety issues occurred requiring emergency unblinding. One patient in the treatment arm had accidental removal of both catheters on POD2 when standing to ambulate and declined replacement of catheters. The remaining treatment arm participants completed the study protocol. In the control arm, 3/32 (9%) experienced intolerable pain and had the ESP catheters and study protocol discontinued. Two patients had accidental dislodgement of one catheter but requested to continue participation and completed the study with one catheter.

Total opioid consumption (POD0-5, morphine equivalents) was not significantly different between the treatment group (142 +/- 151mg, range 0-670mg) and the control group (185 +/- 180mg, range 16-716mg) ($p = 0.33$).

Median and maximum pain scores were similar between groups over POD0-5 (median pain 1.7 +/- 0.3 in the treatment group vs 1.8 +/- 0.5 in the control group, $p = 0.88$; maximum pain 4.4 +/- 1.4 in the treatment group vs 5.2 +/- 1.5 in the control group, $p = 0.4$).

The treatment group had 0/28 (0%) patients with intolerable pain versus 3/32 (9%) in the control group ($p = 0.16$). The treatment group had 3/28 (11%) patients who required no opioids in the postoperative period versus 0/32 (0%) in the control group ($p = 0.11$)

In general, patients showed peak increase in both pro- and anti-inflammatory cytokine levels immediately postoperatively with partial, but not complete, resolution towards baseline levels by POD 2. Patients in the lidocaine arm of the trial had significantly higher anti-inflammatory IL-10 levels immediately postoperatively (73.8 +/- 109.4pg/ml vs 38.3 +/- 31.5pg/ml, $p=0.04$). Levels of proinflammatory IL-6, IL-1b, TNFa, and IFNy were similar between the treatment and control groups.

In both the treatment and control groups, patients with lower preoperative ratios of IL-6 to IL-10 used less total postoperative opioids POD1-POD5. The patients in the lowest quartile of preoperative IL-6/IL-10 used 78.7 +/- 75.1mg morphine equivalents versus the patients in the highest quartile of IL-6/IL-10 used 196.9 +/- 187.5mg morphine equivalents, $p=0.03$.

Discussion

Preliminary analysis of the RACER study demonstrated no difference between total postoperative opioid consumption, median pain scores, or maximum pain scores for patients receiving lidocaine via ESP catheters versus patients with placebo ESP catheters. While not statistically significant given the sample

size, the fact that 11% of patients who received ESP catheters were able to have an opioid-free recovery after open heart surgery should prompt additional inquiry.

The relative increase in serum levels of IL-10 immediately postoperatively in patients treated with lidocaine through the ESP catheter is consistent with animal data showing that IV lidocaine increased production of IL-10 in mechanically ventilated mice.5 This result suggests that lidocaine may exert an anti-inflammatory effect in humans through upregulation of IL-10.

Lower baseline ratios of proinflammatory IL-6 to anti-inflammatory IL-10 were associated with less postoperative opioid usage. This result may provide opportunity to use precision medicine to preoperatively identify patients who may have unique postoperative care needs or to even intervene to modify the pro- vs anti-inflammatory cytokine balance prior to surgery to improve outcomes. Ongoing analysis will examine the duration of mechanical ventilation, ICU and hospital length of stay, as well as time to return of bowel function and pro- and anti-inflammatory biomarker expression and resolution trajectories.

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Disclosures

No

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