Post-operative pain control with extended-release bupivacaine formulation. Clinical Trial Results in Inguinal Hernia Repair.


Introduction

SABER™-Bupivacaine (POSIDUR™) is a semi- viscous solution of sucrose acetate isobutyrate formulation containing 12% bupivacaine, an amide-type local anesthetic. SABER-Bupivacaine, created by DURECT Corporation, is intended to provide prolonged post-surgical pain relief, reduce reliance on opioid analgesic medications, and improve post-operative recovery by slowly releasing bupivacaine over a period of several days. Continuous infusions of local anesthetics into the surgical wound utilizing various catheter and pump systems have demonstrated clinical utility and clinical outcomes in a variety of surgical procedures. SABER-Bupivacaine is designed to provide prolonged release of bupivacaine to local tissues where it is applied. Clinical trials in different surgical settings are ongoing to evaluate and record all clinically significant abnormalities. In a subset of patients continuous ECG monitoring for the placebo patients was 2.7 hours versus >72 hours for the SABER-Bupivacaine 5.0 mL group (p=0.0197). Reduction trends of opioid consumption were supportive for the lower SABER-Bupivacaine dose group, but did not reach statistical significance.

SABER-Bupivacaine 5.0 mL deposited directly at the surgical site was safe and effective in the management of pain in patients who underwent elective, open, unilateral, tension-free, inguinal hernia repair under general anesthesia. The surgical site healed as expected and local tissue conditions were normal in most patients at all time points evaluated. Long term effects on wound-healing were being evaluated at 3 and 6 month follow-up visits via study protocol extension.

Conclusions

• SABER-Bupivacaine 5.0 mL deposited directly at the surgical site was safe and effective in the management of pain in patients who underwent elective, open, unilateral, tension-free, inguinal hernia repair under general anesthesia.

Opioid-Sparing Effects

Patients in all treatment groups had access to opioid analgesic medications. All opioid medications were converted to Morphy Equivalents doses for analysis. Overall, opioid rescue analgesia surgery after surgery was used in 53% (25/47; 95% CI: 38.1%, 67.9%) of patients in the SABER-Bupivacaine 5.0 mL group, 72% (31/43; 95% CI: 59.3%, 84.4%) of patients in the SABER-Bupivacaine 2.5 mL group, and 71% (23/32; 95% CI: 53.3%, 86.3%) of patients in the placebo group. Reduction of percentage of patients resorting to rescue analgesics in the higher dose group labeled not statistically significant, was positively correlated with reduction in daily opioid use. Secondary endpoints to measure opioid consumption in the placebo group were met at a statistically significant level. During the periods of 1-24 hours and 48-72 hours from the placement of SABER-Bupivacaine 2.5 mL, and placebo the positive trend (not statistically significant).

Methodology

Study Design: mult centered, randomized, double-blind, parallel-group, placebo controlled, dose-finding, close-eligibility. All study staff and patients were blinded to the study treatment throughout the study. Participants: male and female patients, in good general health, 18 to 65 years of age, who were undergoing elective open unilateral tension-free Lichtenstein-type inguinal hernia repair under general anesthesia.

Drug administration: at the surgical site prior to the wound closure. Outcome Measures: pain intensity on movement evaluated using a numerical rating scale (0 = no pain; 10 = worst pain possible), collected 4 times a day. The adapted modified Brief Pain Inventory was completed once daily, including symptoms questionnaire of opioid-related side effects and early signs of bupivacaine toxicity. Surgical site healing and local tissue conditions were evaluated at follow-up visits. Vital signs, hemoglobin, and drug concentrations were performed as part of safety assessments. A 12-lead ECG was performed at screening and when clinically indicated to evaluate and record all clinically significant abnormalities. In addition, upon request of patients continuous ECG monitoring for 24 hours postoperatively was performed (n=31) and analyzed postoperatively. Sample Size: 120 evaluable subjects in three treatment groups: SABER-Bupivacaine 2.5 mL (n=42), SABER-Bupivacaine 5.0 mL (n=47), and SABER-Placebo (n=31). It was anticipated that a relative treatment effect of 67% would be detected based on the Mean Pain Intensity on Movement AUC over the time of 1 to 72 hours with 80% power, based on a 5% significance level.

Endpoints: There were no serious adverse events (SAEs) designated by investigators on movement as compared to placebo from 1 to 72 hours (mean 2.47 vs. 3.60; p=0.0033), and from 1 to 48 hours (mean 2.52 vs. 3.86; p=0.007), while the difference between SABER-Bupivacaine 2.5 mL and placebo supported the positive trend (not statistically significant).

Toxicity Monitoring

Bupivacaine pharmacokinetics is important for understanding systemic exposure and prevention of overdose. Rapid rise of plasma concentration (usually after IV injection) and high plasma levels (>2,000 ng/ml), are associated with severe adverse neurologic and then cardiovascular effects in humans (Barbiani et al, 1996; Chubut et al, 1997; Jorfeldt et al, 1968).

Pharmacokinetics of SABER-Bupivacaine were characterized by maintenance of plasma bupivacaine concentrations below toxic levels, mean Cmin, 866.7 ± 226.31 ng/ml, and 886.7 ± 428.61 mg/ml, for 2.5 mL, and 5 mL, respectively. Levels were positively correlated with the daily dose administered. No burst of drug delivery indicated to evaluate and record all clinically significant abnormalities. In addition, upon request of patients continuous ECG monitoring for 24 hours postoperatively was performed (n=31) and analyzed postoperatively. Sample Size: 120 evaluable subjects in three treatment groups: SABER-Bupivacaine 2.5 mL (n=42), SABER-Bupivacaine 5.0 mL (n=47), and SABER-Placebo (n=31). It was anticipated that a relative treatment effect of 67% would be detected based on the Mean Pain Intensity on Movement AUC over the time of 1 to 72 hours with 80% power, based on a 5% significance level.

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Positive trends were also demonstrated with normalized AUC of pain intensity at rest for the same time periods. Most patients in each treatment group were satisfied or very satisfied with treatment, and mean scores for each functional activity improved from Day 1 to 5 in all 3 treatment groups.

In addition, the median time to first use of supplemental opioid analgesic medications after surgery, calculated using Log-Rank test for comparison of Kaplan-Meier survival curves, for the placebo patients was 2 hours versus >72 hours for SABER-Bupivacaine 5.0 mL group (p=0.0197). Reduction trends of opioid consumption were supportive for the lower SABER-Bupivacaine dose group, but did not reach statistical significance. Clinically, reduction of opioid consumption translated into lower incidence of opioid-related side effects. Symptoms typically associated with opioid use reported during the trial were constipation, somnolence, dizziness, nausea and vomiting. A gradual reduction of frequency of each of these symptoms was observed with increase of SABER-Bupivacaine dose. The most frequent symptom, constipation, was reduced significantly as compared between 5.0 mL SABER-Bupivacaine dose and placebo, p=0.0034 (Chi-Square test).

In the 1-48 hours period, the difference in mean pain intensity AUC from the baseline was statistically significant at 2.0 (p=0.0034) for the same time periods. Positive correlation between frequency and dose of opioid consumption and reduction trends of opioid-related adverse events indicates the clinically important opioid-sparing property of SABER-Bupivacaine.

Kaplan Meier (Log Rank test) 1-48 hours

Kaplan Meier (Log Rank test) 1-72 hours

General Safety

There were no serious adverse events (SAEs) designated by investigators on movement as compared to placebo from 1 to 72 hours (mean 2.47 vs. 3.60; p=0.0033), and from 1 to 48 hours (mean 2.52 vs. 3.86; p=0.007), while the difference between SABER-Bupivacaine 2.5 mL and placebo supported the positive trend (not statistically significant). Positive trends were also demonstrated with normalized AUC of pain intensity at rest for the same time periods. Most patients in each treatment group were satisfied or very satisfied with treatment, and mean scores for each functional activity improved from Day 1 to 5 in all 3 treatment groups.

Conclusions

• SABER-Bupivacaine 5.0 mL deposited directly at the surgical site was safe and effective in the management of pain in patients who underwent elective, open, unilateral, tension-free, inguinal hernia repair.

For information regarding SABER-Bupivacaine clinical development, please contact:

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