Treatment of Postoperative Pain in Shoulder Surgery With SABER®-Bupivacaine

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INTRODUCTION

- Early postsurgical pain typically peaks on the first postoperative day with little improvement in the first 72 hours[1,2]
  - Therefore, many surgical procedures performed under general anesthesia require complex postoperative pain management involving opioids, but up to 80% of patients experience an opioid-related adverse event (AE)[3]
- Local anesthetics can significantly reduce pain after surgery, but the short duration (4-24 hours) of most provides little relief past the first postoperative day[4,5]
- SABER-Bupivacaine (sucrose acetate isobutyrate extended release-bupivacaine) is a semiviscous solution that contains the active ingredient bupivacaine (132 mg/mL) in a delivery platform composed of a biodegradable organic matrix and the solvent benzyl alcohol[6]
  - On instillation, the solvent diffuses leaving an extended-release, in situ depot that delivers the local anesthetic at the surgical site throughout the first 72 postoperative hours
- SABER-Bupivacaine is intended to provide prolonged pain relief after surgery, reduce reliance on opioid analgesic medications, and improve postoperative recovery by slowly releasing bupivacaine for 72 hours[6]
- The trial presented was conducted to evaluate SABER-Bupivacaine treatment for postoperative pain in patients undergoing arthroscopic subacromial decompression[6]

METHODS

Study Design and Treatment

- This was an international, parallel-group, randomized, double-blind, active- and placebo-controlled phase 2 trial in 107 adult patients (≥18 years of age) undergoing elective arthroscopic shoulder surgery[6]
- Patients were randomly assigned in a 2:1:1 allocation ratio to the following 3 treatment arms[6]
  - 5 mL SABER-Bupivacaine (660 mg bupivacaine; n = 53)
  - 5 mL SABER-placebo (n = 25)
  - 20 mL standard bupivacaine hydrochloride (HCl) (50 mg bupivacaine; n = 29)
- Arthroscopic subacromial decompression was performed on day 0; entry to the subacromial space was through 3 to 4 standard portals under general anesthesia[6]
  - On completion of the shoulder surgery, a single dose of treatment medication was deposited subacromially under direct vision with the arthroscope
- All patients received paracetamol (4 g/day) as background treatment. If pain was not sufficiently relieved, patients were allowed rescue medication in the form of morphine (oral or intravenous [IV]) from day 0 to 72 hours after surgery[6]

Study End Points

- The coprimary end points were pain intensity on shoulder movement time-normalized area under the curve during the period 1 to 2 hours after surgery (AUC_{1-72}) and total use of opioid rescue analgesia 0 to 72 hours after surgery[6]
  - Pain intensity was measured at rest or on movement (flexion of the shoulder to 90°) using the 11-point Numeric Rating Scale at screening, on day 0 at 1, 2, 4, 6, 8, and 12 hours after surgery, and on days 1 to 7 after surgery at 8 AM, 12 PM, 4 PM, and 8 PM
  - Total opioid rescue analgesic use from 0 to 72 hours after surgery was measured as IV morphine equivalent doses computed for the first 6-hour period and every 12-hour period thereafter
- Key secondary end points included[6]
  - Time to first opioid rescue medication use (hours)
  - Pain intensity at rest AUC over the period 1 to 72 hours after surgery
- Safety was examined by monitoring AEs; assessing laboratory test results, physical examination findings, vital signs, and surgical wound healing; and evaluating electrocardiography, MRI, and constant functionality tests to determine shoulder function (all conducted before and after surgery [MRI and physician examination conducted up to 6 months after surgery])

RESULTS

Study Patients

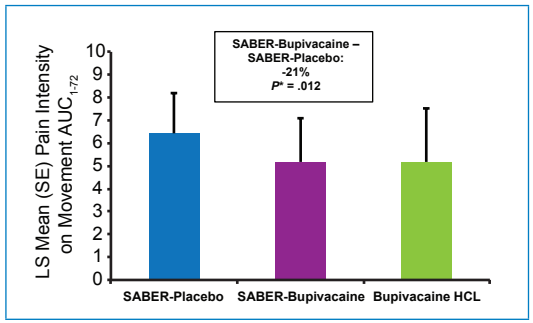
Table 1. Patient Demographics and Baseline Characteristics (ITT population)

	SABER-Bupivacaine n = 53	Bupivacaine HCl n = 29	SABER-Placebo n = 25	Total N = 107
Age, years, mean (SD)	50.1 (9.5)	51.6 (10.7)	48.6 (10.1)	50.2 (9.9)
Sex, n (%)				
Male	20 (37.7%)	12 (41.4%)	11 (44.0%)	43 (40.2%)
Female	33 (62.3%)	17 (58.6%)	14 (56.0%)	64 (59.8%)
Race, n (%)				
White	50 (94.3%)	29 (100%)	24 (96.0%)	103 (96.3%)
Hispanic	2 (3.8%)	0	0	2 (1.9%)
Asian	0	0	1 (4.0%)	1 (0.9%)
Other	1 (1.9%)	0	0	1 (0.9%)
Mean BMI (range)	26.77 (20.3-35.3)	26.65 (21.5-41.5)	25.38 (19.3-34.5)	25.52 (19.3-41.5)

Efficacy Outcomes

- The coprimary end point of mean pain intensity on movement AUC for the time period 1 to 72 hours after surgery was 5.16 (±1.94 SD) for the SABER-Bupivacaine group, 6.43 (±1.77 SD) for the SABER-placebo group, and 5.16 (±2.38 SD) for the standard bupivacaine HCl group (**Figure 1**)

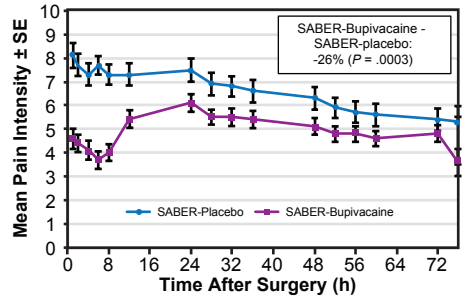
Figure 1. Mean pain intensity on movement (AUC_{1-72}) (LOCF; ITT population).



ANOVA, analysis of variance; AUC_{1-72}, area under the curve during the period 1 to 2 hours after surgery; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; SE, standard error.
Error bar = standard deviation.
*P-value derived from ANOVA with treatment and pooled sites as main effects.

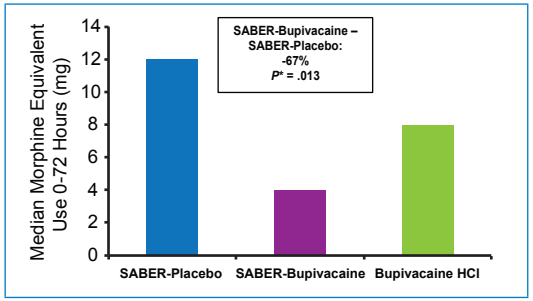
- In a repeated-measures pain intensity on movement analysis, SABER-Bupivacaine significantly reduced pain intensity by 26% compared with SABER-placebo ($P = .0003$)[6] (**Figure 2**)

Figure 2. Repeated-measures pain intensity on movement (ITT population).



- Rescue medication use was significantly reduced in patients treated with SABER-Bupivacaine compared with SABER-placebo (Wilcoxon $P = .013$), with median morphine equivalents of 4 mg for SABER-Bupivacaine, 8 mg for standard bupivacaine HCl, and 12 mg for SABER-placebo over 72 hours[6] (**Figure 3**)

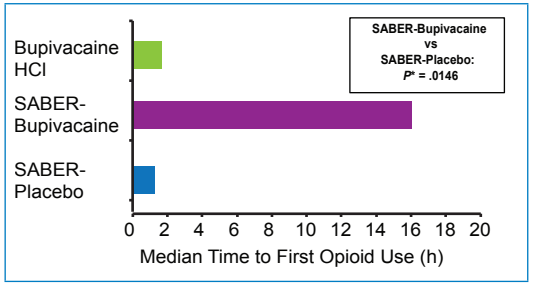
Figure 3. Rescue opioid medication use (based on nonparametric test; ITT population).



*P-value derived from nonparametric Wilcoxon rank-sum test.

- Median time to first opioid rescue medication use (based on the Friedman test) was 16 hours for SABER-Bupivacaine compared with 1.3 hours for SABER-placebo ($P = .015$) and 1.7 hours for standard bupivacaine HCl[6] (**Figure 4**)

Figure 4. Median time to first rescue opioid medication (log-rank test; ITT population).



*P-value derived from log-rank test.

Safety

- All patients completed the trial normally (no discontinuations/withdrawals), and the incidence of treatment-emergent AEs (TEAEs) was similar between treatment groups[6]
- The most frequent TEAEs were headache, nausea, and musculoskeletal pain (4.7% of total patients for each)[6] (**Table 2**)
  - Most TEAEs were reported as mild or moderate in intensity (no notable differences between treatment groups with regard to intensity)

Table 2. Summary of TEAEs Occurring in ≥2% of Total Patients (safety population)

n (%)	SABER-Bupivacaine n = 53	SABER-Placebo n = 25	Bupivacaine HCl n = 29	Total N = 107
Headache	3 (5.7)	1 (4.0)	1 (3.4)	5 (4.7)
Nausea	1 (1.9)	3 (12.0)	1 (3.4)	5 (4.7)
Musculoskeletal pain	2 (3.8)	1 (4.0)	2 (6.9)	5 (4.7)

- Surgical site healing and/or local tissue conditions evaluated by MRI were as expected in all patients examined at day 7, at trial end, and at the 6-month follow-up visit
- Overall, no signal indicating an increased cardiac risk for patients exposed to either SABER-Bupivacaine or standard bupivacaine HCl was observed

CONCLUSIONS

- SABER-Bupivacaine significantly reduces pain intensity compared with SABER-placebo throughout the first 72 hours after surgery
  - Additionally, SABER-Bupivacaine was shown to be statistically superior to standard bupivacaine HCl and SABER-placebo in a repeated-measures pain intensity on movement analysis for the period of 1 to 24 hours after surgery
- SABER-Bupivacaine was shown to significantly reduce rescue opioid use and prolonged median time to first rescue opioid medication compared with SABER-placebo for 0 to 72 hours after surgery
- SABER-Bupivacaine, standard bupivacaine HCl, and SABER-placebo were generally safe and well tolerated
- Taken together, these results indicate that patients treated with SABER-Bupivacaine experienced significantly less pain and required significantly less rescue medication throughout the first 72 hours after shoulder surgery than did those who received SABER-placebo

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