SABER®-Bupivacaine Reduces Postoperative Pain Intensity and Opioid Use for 72 Hours in Soft-Tissue and Bony Surgeries

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INTRODUCTION

- Early postsurgical pain typically peaks within 24 hours after surgery and continues for a period of 72 hours[1]
- Complex postoperative pain management involving the use of opioids may be necessary after surgical procedures performed under general anesthesia, but up to 80% of patients experience an opioid-related adverse event (AE)[2]
  - Opioid-related AEs can extend the length of hospital stay and increase the likelihood of readmission[3]
  - ~5% of patients on opioids abuse them at least 90 days after first use[3]
- Local anesthetics have been shown to reduce pain after surgery, but their duration of action is 24 hours at most, and hence they provide little pain relief beyond the first postoperative day[4]
  - There is an unmet need for a simple-to-use, nonopioid treatment option that provides reliable pain relief over the postsurgical 72-hour period, regardless of surgery type
- SABER-Bupivacaine is an extended-release formulation of bupivacaine designed to provide prolonged postsurgical local analgesia up to 72 hours after single-dose administration
  - It is a semiviscous mixture of 12% bupivacaine, which is an amide-type local anesthetic, the solvent benzyl alcohol, and sucrose acetate isobutyrate (SAIB)[5]
- SABER-Bupivacaine has been designed to provide prolonged pain relief after surgery, reduce reliance on opioid analgesic medications, and improve recovery after surgery by slowly releasing bupivacaine over several days[5]

OBJECTIVE

- To evaluate the efficacy, safety, and dose-response of SABER-Bupivacaine compared with SABER-placebo following soft-tissue and bony-tissue surgeries[5,6]

METHODS

Study Designs

- 2 randomized, double-blind, placebo-controlled trials enrolling patients undergoing either soft-tissue (unilateral tension-free inguinal hernia repair) or bony (arthroscopic subacromial decompression [ASD]) surgery

Inguinal Hernia Repair Study

- Eligible patients were undergoing inguinal hernia repair using the standard tension-free Lichtenstein technique[1] under general anesthesia
- All patients were randomized (3:3:2) to receive one of the following:
  - 2.5 mL of SABER-Bupivacaine (12% wt/wt, 132 mg/mL bupivacaine)
  - 5 mL of SABER-Bupivacaine
  - 2.5 or 5 mL of SABER-placebo
- Half the treatment dose was instilled into the wound; after closure of the aponeurosis, the next half was administered into the wound
- Rescue medication was allowed for all patients
  - For moderate to severe pain: intravenous (IV) or oral tramadol 50 to 100 mg (maximum, 400 mg per day)
  - For mild to moderate pain: acetaminophen 1 g 4× per day
- Primary efficacy end points were mean pain intensity on movement-time–normalized area under the curve (AUC) during the first 72 hours after surgery and proportion of patients receiving opioid rescue medication
  - IV morphine equivalent dose over 72 hours and safety evaluations were secondary end points

Arthroscopic Subacromial Decompression Surgery Study

- Patients were randomly assigned in a 2:1:1 allocation ratio to the following 3 treatment arms[5]
  - 5 mL of SABER-Bupivacaine (660 mg bupivacaine)
  - 5 mL of SABER-placebo
  - 20 mL of standard bupivacaine HCl (50 mg bupivacaine)
- Arthroscopic subacromial decompression surgery was performed on day 0; entry to the subacromial space was through 2 to 3 standard portals under general anesthesia[5]
  - On completion of the shoulder surgery, a single dose of treatment medication was instilled subacromially
- 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 IV) from 0 to 72 hours after surgery[5]
- The coprimary end points were pain intensity on shoulder movement during the period 1 to 72 hours after surgery (AUC_{1-72}) and total use of opioid rescue analgesia 0 to 72 hours after surgery[5]
  - Key secondary end points were time to first opioid rescue medication use (hours), pain intensity at rest AUC_{1-72}, and safety evaluations

Statistical Analysis

- Scheduled pain intensity on movement from 0 to 72 hours after surgery was analyzed by repeated measures ANOVA with treatment, time as main effect and the interaction of treatment and time; least squares means were compared between treatment groups
- Morphine use from 0 to 72 hours and by each day were analyzed by Wilcoxon rank-sum test

Patient Demographics

- Patient characteristics and baseline demographics are shown in **Tables 1 and 2**

Table 1. Baseline and Demographic Characteristics: Inguinal Hernia Repair Study

	SABER-Bupivacaine 5 mL n = 47	SABER-Placebo n = 32
Age, years, mean (SD)	48.6 (13.0)	50.3 (9.3)
Sex, n (%)		
Male	45 (95.7)	32 (100.0)
Female	2 (4.3)	0
Race, n (%)		
White	46 (97.9)	30 (93.8)
Mixed	0	1 (3.1)
Black	0	1 (3.1)
Other	1 (2.1)	0
BMI, kg/m^2, mean (range)	26.3 (19-33)	26.9 (20-36)

BMI, body mass index; SD, standard deviation.

Table 2. Baseline and Demographic Characteristics: ASD Surgery Study

	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%)
BMI, kg/m^2, mean (range)	26.8 (20.3-35.3)	26.7 (21.5-41.5)	25.4 (19.3-34.5)	25.5 (19.3-41.5)

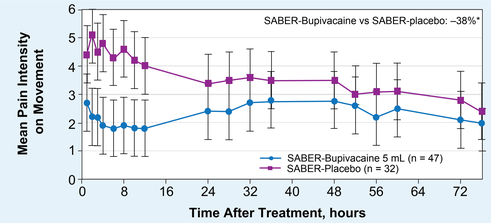
BMI, body mass index; ITT, intent-to-treat; SD, standard deviation.

RESULTS

Efficacy End Points

- In patients undergoing inguinal hernia repair surgery, mean pain intensity was significantly lower in patients receiving SABER-Bupivacaine compared with those receiving SABER-placebo (**Figure 1**)

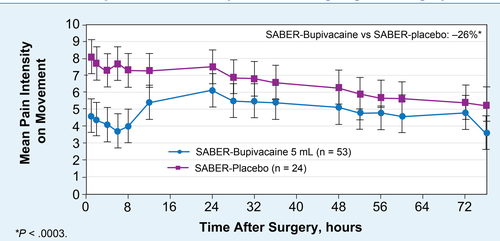
Figure 1. Pain intensity on movement in patients undergoing inguinal hernia repair surgery.



*P < .0001 when comparing overall least squares means.
Pain intensity was evaluated on a 10-point scale

- In patients undergoing ASD surgery, mean pain intensity was significantly lower in patients receiving SABER-Bupivacaine compared with those receiving SABER-placebo (**Figure 2**)

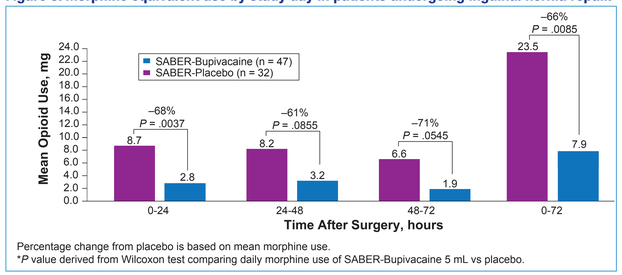
Figure 2. Pain intensity on movement in patients undergoing ASD surgery.



*P < .0003.
There was no statistical significance between SABER-Bupivacaine and Bupivacaine-HCl (data not shown).

- In patients undergoing inguinal hernia repair, supplemental opioid use was lower in the SABER-Bupivacaine group compared with the SABER-placebo group[6] (**Figure 3**)

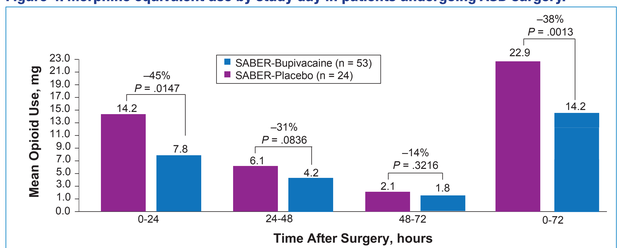
Figure 3. Morphine equivalent use by study day in patients undergoing inguinal hernia repair.



Percentage change from placebo is based on mean morphine use.
*P value derived from Wilcoxon test comparing daily morphine use of SABER-Bupivacaine 5 mL vs placebo.

- In patients undergoing ASD surgery, supplemental opioid use was lower in the SABER-Bupivacaine group compared with the SABER-placebo group[5] (**Figure 4**)

Figure 4. Morphine equivalent use by study day in patients undergoing ASD surgery.



There was no statistically significant difference between SABER-Bupivacaine and Bupivacaine-HCl (data not shown).
Percentage change from placebo is based on the mean morphine use.
*P value derived from Wilcoxon test comparing daily morphine use of SABER-Bupivacaine 5 mL vs placebo.

CONCLUSIONS

- SABER-Bupivacaine significantly decreased mean pain intensity on movement compared with SABER-placebo for 72 hours after surgery in patients undergoing inguinal repair and ASD surgery
- SABER-Bupivacaine also significantly reduced the use of rescue opioid medication compared with SABER-placebo for the first 72 hours after surgery with meaningful reduction on each day
- The effects of SABER-Bupivacaine were well maintained over the 72-hour observation period
- These results indicate that patients treated with SABER-Bupivacaine experienced significantly less pain and required significantly less rescue medication during the first 72 hours compared with patients treated with SABER-placebo, regardless of surgery type

DISCUSSION

- SABER-Bupivacaine may provide a simple-to-use foundation for reliable, continuous 72-hour pain relief in a variety of surgeries to help spare opioid use and its corresponding adverse events
- SABER-Bupivacaine has the potential to improve recovery and reduce readmissions and call-backs due to inadequate pain relief or opioid-related adverse events

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