Efficacy and Safety of SABER®-Bupivacaine Local Anesthetic in Open Hernia Repair

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INTRODUCTION

- Early postsurgical pain typically peaks in the first 24 hours and continues for the first 72 hours[1,2]
- 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)[3]
- Local anesthetics have been shown to significantly reduce pain after surgery, but most have a very short duration of action (4-24 hours) that provides little relief past the first postoperative day[4,5]
- SABER-Bupivacaine is a semiviscous mixture of 12% bupivacaine, which is an amide local anesthetic, sucrose acetate isobutyrate (SAIB) and benzyl alcohol[6]
- 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[6]

OBJECTIVE

- To evaluate the efficacy and safety and dose-response of SABER-Bupivacaine compared with SABER-placebo after inguinal hernia repair[7]

METHODS

Study Design

- This was a double-blind, placebo-controlled, dose-finding, phase 2 study of SABER-Bupivacaine in patients undergoing inguinal hernia repair using the standard tension-free Lichtenstein technique[1] under general anesthesia, conducted at 5 centers in Australia and New Zealand
- Eligible patients were randomly assigned (3:3:2) to receive 2.5 mL or 5 mL SABER-Bupivacaine (12% wt/wt, 132 mg/mL bupivacaine) or SABER-placebo (2.5 or 5 mL)
- Half the treatment dose was instilled in the sub-aponeurotic space; after closure of the aponeurosis, the remaining half was instilled into the subcutaneous space before final closure of the skin
- Rescue medication was allowed for all patients
  - For moderate to severe pain: IV or oral tramadol 50 to 100 mg (maximum, 500 mg per day)
  - For mild to moderate pain: acetaminophen 1 g 4× per day
- Primary efficacy end points were mean pain intensity on movement normalized area under the curve (AUC) during the first 72 hours after surgery and proportion of patients receiving opioid rescue medication
  - Intravenous morphine equivalent dose over 72 hours was a secondary end point

Eligibility Criteria

Key Inclusion Criteria[6]

- Adults (18-65 years of age) undergoing elective inguinal hernia repair
- Good health based on history, physical examination, and 12-lead electrocardiography (ECG)

Key Exclusion Criteria[6]

- Scar tissue from previous abdominal surgery that could interfere with hernia repair
- High blood pressure
- 12-lead ECG abnormalities
- Use or regular use of analgesic medication

Efficacy and Safety Analyses[6]

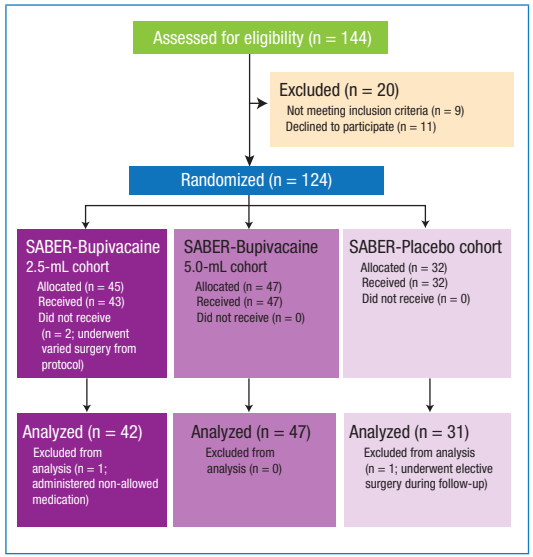
- Pain intensity (at rest and on movement) was assessed before surgery and at regular intervals for the first 5 days after surgery using a 10-point scale, where 0 was no pain and 10 was worst pain possible
- 12-lead ECG was performed during patient screening and on treatment day 1
- Data for the 2.5-mL and 5-mL SABER-placebo groups were combined

RESULTS

Patient Disposition

- 144 patients were screened, 124 patients were randomly assigned, and 123 patients received study treatment[6] (**Figure 1**)
- Safety population: 123 patients who received at least part of a treatment instillation[6]
- ITT population: 122 patients who received full study medication[6]
- Efficacy population: 120 patients who completed the study without major protocol deviations[6]

Figure 1. Patient disposition.[7]



Baseline Demographics

Table 1. Baseline and Demographic Characteristics (ITT population, N = 122)[6]

	SABER-Bupivacaine 2.5 mL n = 43	SABER-Bupivacaine 5 mL n = 47	SABER-Placebo n = 32
Sex, n (%)			
Male	41 (95.3)	45 (95.7)	32 (100.0)
Female	2 (4.7)	2 (4.3)	0
Ethnic group, n (%)			
White	40 (93.0)	46 (97.9)	30 (93.8)
Mixed	2 (4.7)	0	1 (3.1)
Black	0	0	1 (3.1)
Hispanic/Latino	1 (2.3)	0	0
Other	0	1 (2.1)	0
Age, years			
Mean (SD)	46.1 (11.88)	48.6 (13.04)	50.3 (9.26)
Range	20-67	21-79	27-65
BMI, kg/m^2			
Mean (SD)	26.6 (3.78)	26.3 (2.92)	26.9 (3.68)
Range	20-39	19-33	20-36

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

Efficacy End Points

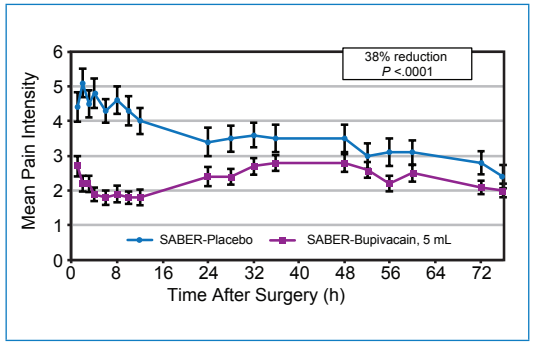
- Mean pain intensity on movement-normalized AUC_{1-72} was significantly improved in the 5-mL SABER-Bupivacaine group compared with the SABER-placebo group (analysis of variance)[6] (**Table 2, Figure 2**)

Table 2. Summary of Pain Intensity Results (ITT population, N = 122)[6]

	SABER-Bupivacaine 2.5 mL n = 43	SABER-Bupivacaine 5 mL n = 47	SABER-Placebo n = 32
Pain intensity on movement AUC_{1-72} (including opioid rescue pain)			
LS mean (SE)	3.4 (0.26)	2.7 (0.25)	3.9 (0.29)
LS mean difference from SABER-placebo	–0.53 (0.359)	–1.14 (0.353)	—
P-value	.2372	.0031	—

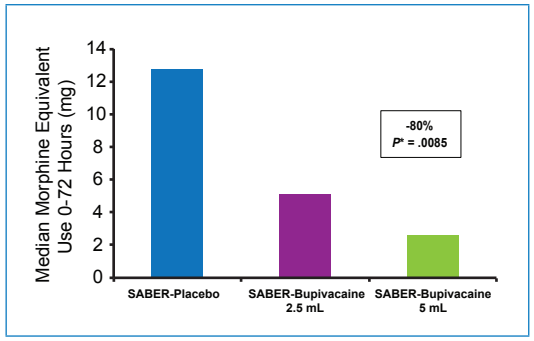
- Mean pain intensity was improved each day in the 5-mL SABER-Bupivacaine group compared with the SABER-placebo group[6] (**Figure 2**)

Figure 2. Pain intensity on movement: repeated-measures analysis (ITT population, N = 122).[6]



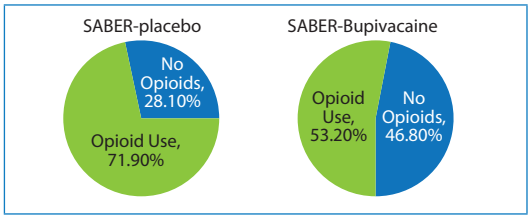
- Supplemental opioid use also decreased in the 5-mL SABER-Bupivacaine group compared with the SABER-placebo group[6] (**Figure 3**)
  - Opioid use also decreased in the 2.5-mL SABER-Bupivacaine group compared with the SABER-placebo group but did not reach statistical significance

Figure 3. Morphine equivalent use for 0 to 72 hours (ITT population, N = 122).[6]



*P-value vs SABER-placebo; P-value is derived from nonparametric Wilcoxon rank-sum test.

Figure 4. Opioid use after surgery in patients given 5 mL SABER-Bupivacaine and patients given SABER-placebo (ITT population, N = 122).[6]



ITT, intent-to-treat.

- Wound healing was normal in all patients 6 months after surgery[6]

Safety

- Most common AEs were reported to a similar extent across treatment groups[6] (**Table 4**)
- Opioid-related AEs, such as constipation (27.7% vs 56.3%), dizziness (23.4% vs 31.1%), and nausea (19.1% vs 31.1%), were reported less frequently in the 5-mL SABER-Bupivacaine group than in the SABER-placebo group, respectively[6]

Table 4. AEs Occurring in >10% of Each Treatment Group (safety population, N = 123)[6]

AEs, n (%)	SABER-Bupivacaine 2.5 mL n = 44	SABER-Bupivacaine 5 mL n = 47	SABER-Placebo n = 32
Somnolence	20 (45.5)	18 (38.3)	16 (50.0)
Constipation[a]	17 (38.6)	13 (27.7)	18 (56.3)
Bradycardia	9 (20.5)	12 (25.5)	7 (21.9)
Dizziness	14 (31.8)	11 (23.4)	10 (31.3)
Pruritus	13 (29.5)	11 (23.4)	7 (21.9)
Application Site Discoloration	10 (22.7)	11 (23.4)	6 (18.8)
Nausea	14 (31.8)	9 (19.1)	10 (31.3)
Headache	11 (25.0)	9 (19.1)	7 (21.9)
Paresthesia	9 (20.5)	5 (10.6)	2 (6.3)
Dysgeusia	6 (13.6)	5 (10.6)	5 (15.6)
Tinnitus	3 (6.8)	6 (12.8)	5 (15.6)

[a]P = .0106, chi-square (5 mL SABER-Bupivacaine compared with 5 mL SABER-placebo).

Bradycardia, heart rate measured <40 beats per minute; dysgeusia, subjective impaired sense of taste.

CONCLUSIONS

- SABER-Bupivacaine significantly decreased the coprimary end point of mean pain intensity on movement compared with SABER-placebo for the first 72 hours after surgery and during each 24-hour period
- SABER-Bupivacaine also significantly reduced the use of rescue opioid medication compared with SABER-placebo for the first 72 hours after surgery
- SABER-Bupivacaine and SABER-placebo were generally safe and well tolerated
  - Patients receiving SABER-Bupivacaine experienced fewer opioid-related AEs
- These results indicate that patients treated with SABER-Bupivacaine experienced significantly less pain and required significantly less rescue medication during the first 72 hours, including the 24- to 72-hour time frame, after hernia surgery compared with patients treated with SABER-placebo

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