Poster #2168

SABER®-Bupivacaine Reduces Postoperative Pain and Opioid Consumption Following Arthroscopic Subacromial Decompression

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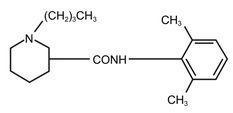
INTRODUCTION

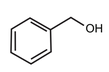
- The role of local anesthetics in postoperative analgesia is limited by their relatively short durations of action[1-5]
- **Sucrose acetate isobutyrate extended-release bupivacaine (SABER®-Bupivacaine)** is:
  - An investigational long-acting analgesic formulation containing bupivacaine 660 mg (13.2% wt/vol) in a single 5 mL dose (**Figure 1**)
  - Designed to release bupivacaine continuously to the surgical site for 3 days after local instillation
- The objective of this study was to determine the efficacy and safety of treatment with SABER-Bupivacaine in reducing pain and opioid consumption following arthroscopic subacromial decompression

Figure 1. SABER-Bupivacaine

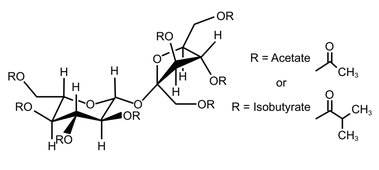
12% bupivacaine
- Active analgesic
- 660 mg in single 5 mL dose
- Released at approximately 10 mg/h for 72 h



22% benzyl alcohol
- Antimicrobial solvent



66% SAIB (sucrose acetate isobutyrate)
- Esterified sugar matrix
- Biocompatible/biodegradable
- Stores bupivacaine at high concentrations

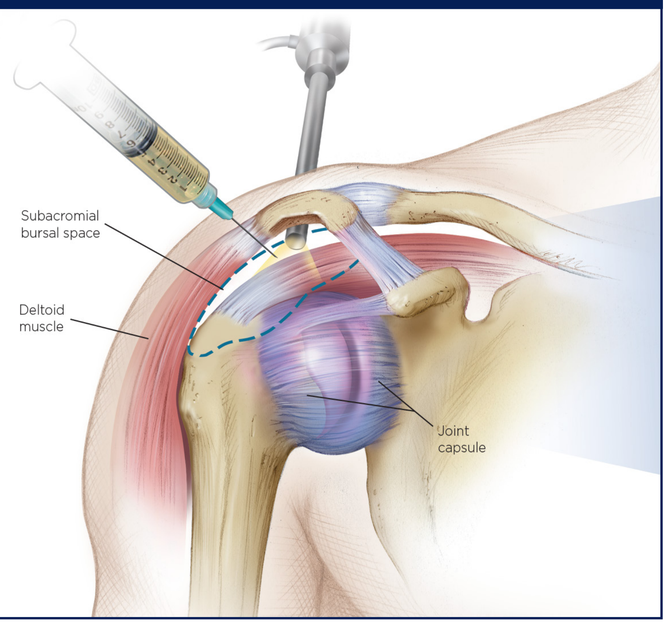


Percentages are wt/wt.

METHODS

- This randomized, double-blind, placebo- and active-controlled trial was conducted at 9 sites in Austria, Denmark, Germany, Latvia, and Sweden
- Patients aged ≥18 years with MRI-confirmed intact rotator cuffs undergoing arthroscopic subacromial decompression under general anesthesia were randomized 2:1:1 to one of the following:
  - SABER-Bupivacaine 5 mL
  - Bupivacaine hydrochloride (HCl) 0.25% 20 mL
  - SABER-placebo 5 mL (SABER formulation without bupivacaine)
- Study drug was percutaneously instilled into the subacromial space under direct arthroscopic visualization at the close of surgery (**Figure 2**)

Figure 2. Instillation



- Patients rated pain intensity on movement (90° shoulder flexion) on an 11-point numerical rating scale that ranged from 0 (no pain) to 10 (worst pain imaginable)
- Pain intensity was assessed 6 times on the day of surgery and 4 times per day on the following 7 days
- All patients received paracetamol background treatment (4 g/d for body weight ≥66 kg, 2 g/d for body weight <66 kg) until 72 hours postsurgery
- Morphine (2 mg intravenously [IV] or 10 mg by mouth) was administered on request as rescue medication for breakthrough pain
- Interscalene block was not allowed, so that early postoperative pain assessments could be made and analgesic time of onset assessed
- Key efficacy endpoints included:
  - Pain intensity on movement from 1 to 72 hours after surgery (expressed as time-normalized area under the curve [AUC_{1-72}])
  - Cumulative dose of opioid rescue medication (in IV morphine mg equivalents) from 0 to 72 hours after surgery
  - Time to first use of opioid rescue medication

RESULTS

- All 107 randomized patients received treatment (**Table 1**)

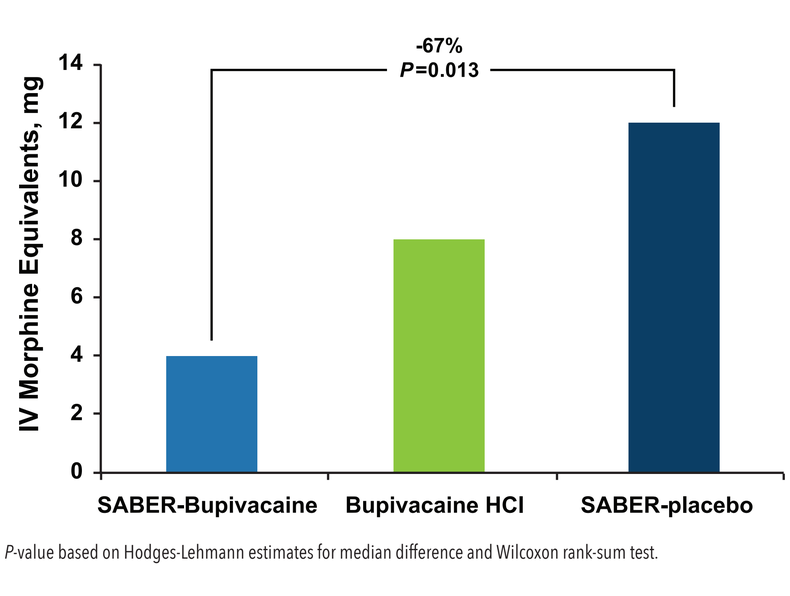
Table 1. Patient Demographics

	SABER-Bupivacaine (n=53)	Bupivacaine HCl (n=29)	SABER-Placebo (n=25)	Total (n=107)
Sex, n				
Female/Male	33/20	17/12	14/11	64/43
Age, years				
Mean (range)	50.1 (28–70)	51.6 (21–70)	48.6 (24–63)	50.2 (21–70)
Race, n				
Asian	0	0	1	1
Hispanic	2	0	0	2
White	50	29	24	103
Other	1	0	0	1
Body Mass Index, kg/m²				
Mean (range)	26.8 (20.3–35.3)	26.6 (21.5–41.5)	25.8 (19.3–34.5)	25.5 (19.3–41.5)

EFFICACY ASSESSMENTS

- Mean (SE) pain intensity AUC_{1-72} was 5.16 (0.27) for SABER-Bupivacaine, 5.16 (0.44) for bupivacaine HCl, and 6.43 (0.35) for placebo (*P*=0.012, SABER-Bupivacaine vs placebo)
- Least squares mean (SE) pain intensity by post hoc mixed-model repeated-measures analysis was 4.6 (0.33) for SABER-Bupivacaine, 5.0 (0.37) for bupivacaine HCl, and 6.2 (0.42) for placebo (*P*=0.0003, SABER-Bupivacaine vs placebo) (**Figure 3**)

Figure 3. Mean Pain Intensity on Movement Following Arthroscopic Subacromial Decompression, 1–72 Hours After Surgery



P-value based on mixed-model repeated-measures ANCOVA.
LS, least squares.

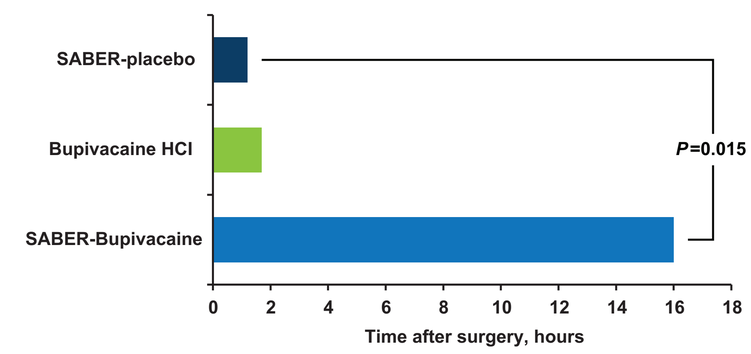
- Median cumulative dose of opioid rescue medication in IV morphine equivalents was 4.0 mg for SABER-Bupivacaine, 8.0 mg for bupivacaine HCl, and 12.0 mg for placebo (*P*=0.013, SABER-Bupivacaine vs placebo) (**Figure 4**)

Figure 4. Median Cumulative Opioid Analgesic Use, 0–72 Hours After Surgery

P-value based on Hodges-Lehmann estimates for median difference and Wilcoxon rank-sum test.

- Median time to first use of opioid rescue medication was 16.0 hours for SABER-Bupivacaine, 1.7 hours for bupivacaine HCl, and 1.3 hours for placebo (*P*=0.015 for SABER-Bupivacaine vs placebo) (**Figure 5**)

Figure 5. Median Time to First Opioid Rescue Medication Use



P-value based on logrank test.

SAFETY ASSESSMENTS

- The incidence of treatment-emergent adverse events (TEAEs), defined as adverse events with onset after study drug administration, was similar between treatment groups: 30.2% for SABER-Bupivacaine, 37.9% for bupivacaine HCl, and 40.0% for placebo (**Table 2**)
- The majority of TEAEs were mild or moderate in severity
- Vital signs, physical exam, electrocardiography, and wound healing assessments were similar between groups

Table 2. TEAEs by Primary System Organ Class That Occurred in >3% of Patients Overall

	SABER-Bupivacaine (n=53)	Bupivacaine HCl (n=29)	SABER-Placebo (n=25)
All TEAEs, n (%)	16 (30.2)	11 (37.9)	10 (40.0)
TEAEs, n			
Nervous system disorders	5	4	2
Headache	3	1	1
Investigations	5	2	2
Alanine aminotransferase increased	1	0	2
Gastrointestinal disorders	2	1	3
Nausea	1	1	3
Cardiac disorders	1	3	2
Musculoskeletal and connective tissue disorders	3	2	1
Musculoskeletal pain	2	2	1
Skin and subcutaneous tissue disorders	2	2	2
Injury and procedural complications	3	0	1
General disorders and administration-site conditions	1	0	2
Respiratory, thoracic, and mediastinal disorders	1	2	0

CONCLUSIONS

- For patients undergoing arthroscopic subacromial decompression, SABER-Bupivacaine significantly reduced postoperative pain intensity for 72 hours compared with placebo
- SABER-Bupivacaine significantly reduced the use of opioid rescue medication and prolonged the median time to first opioid use compared with placebo
- SABER-Bupivacaine, bupivacaine HCl, and placebo were all well tolerated, with no substantial differences in incidence or severity of TEAEs between groups
- SABER-Bupivacaine, a sustained-release, locally acting analgesic, may be a valuable addition to the postoperative pain management arsenal for routine outpatient shoulder arthroscopy

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DISCLOSURES

A. Ekelund has received royalties from, and is a consultant for, DePuy-Synthes
J. Grohs, A. Peredistijs, and S. Rasmussen have nothing to disclose
D. Ellis and N. Verity are DURECT employees

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