Treatment of Postoperative Pain in Major Abdominal Surgery With SABER®-Bupivacaine: Results of the BESST Trial

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INTRODUCTION

- Early postsurgical pain typically peaks on the first postoperative day and shows some improvement over the first 72 hours[1,2]
- Therefore, many surgical procedures performed under general anesthesia require complex postoperative pain management involving the use of strong opioids, but up to 80% of patients experience an opioid-related adverse event[3]
- Although local anesthetics can significantly reduce pain after surgery, the short duration 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]
  - The solvent diffuses on instillation, leaving an extended-release, in situ depot that delivers the local anesthetic at the surgical site throughout the first 72 postoperative hours[6]
- The Bupivacaine Effectiveness and Safety SABER Trial (BESST) was conducted to extend the existing clinical experience with SABER-bupivacaine to patients undergoing major abdominal surgery

METHODS

Study Design and Treatment

- This was an international, multicenter, randomized, double-blind, parallel-group controlled, phase 3 trial in patients undergoing elective major abdominal surgery[1]
- Patients were enrolled into 1 of 3 cohorts, depending on the type of surgical procedure, with a 3:2 allocation ratio of SABER-Bupivacaine to control for all cohorts[1]
  - Cohort 1 patients (n = 48) underwent open laparotomy, and the control was bupivacaine HCl (150 mg)
  - Cohort 2 patients (n = 50) underwent laparoscopic cholecystectomy and the control was bupivacaine HCl (150 mg)
  - Cohort 3 patients (n = 207) underwent laparoscopic-assisted colectomy and the control was SABER-placebo
- SABER was instilled directly into the surgical incisions with a catheter, whereas bupivacaine HCl was infiltrated into the peri-incisional tissue with a hypodermic needle[1]
- In the postoperative period, all patients had access to rescue opioids when pain intensity was rated at ≥4 points on a 0 to 10 numerical rating scale (moderate to severe pain)[1]
  - Pain intensity at rest and on movement (sitting up in bed) was recorded with an electronic device (LogPad; PHT, Boston, MA)
- Safety was monitored by evaluation of vital signs, physical examination findings, safety laboratory test results, and adverse events (AEs) and included cardiovascular and neurologic event monitoring (standard 12-lead ECG at screening and at final visit and 12-lead Holter monitoring before surgery to 72 hours after surgery) and assessment of surgical wound healing (day 7, final visit, and day 30) and local tissue conditions (days 7 and 14)

Primary End Points

- Coprimary end points were mean pain intensity on movement time-normalized area under the curve during the period 0 to 72 hours after dose (AUC_{0-72})—using both scheduled pain intensity and opioid rescue pain intensity—and mean total intravenous morphine-equivalent opioid dose during the period 0 to 72 hours after dose

RESULTS

Study Patients

- The intent-to-treat (ITT) population consisted of 296 randomly assigned patients: 182 patients treated with SABER-Bupivacaine, 37 patients treated with bupivacaine HCl, and 77 patients treated with SABER-placebo (**Table 1**)

Table 1. Surgical Procedural Characteristics (safety population)

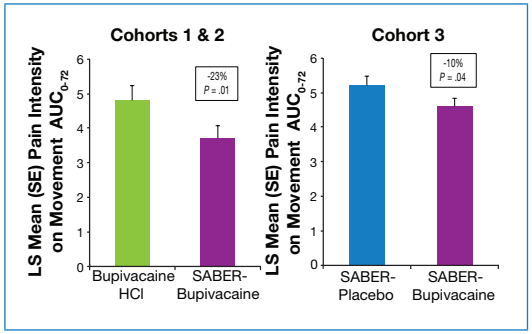
	Cohort 1[a]		Cohort 2[a]		Cohort 3[a]	
	SABER-Bupivacaine n = 30	Bupivacaine HCl n = 18	SABER-Bupivacaine n = 30	Bupivacaine HCl n = 20	SABER-Bupivacaine n = 129	SABER-Placebo n = 78
Cumulative incision length, mean (SD), cm						
	19.6 (7.98)	20.7 (7.53)	3.9 (0.81)	3.8 (0.77)	9.3 (3.39)	8.4 (2.77)
Number of incisions, n (%)						
1	27 (90.0)	16 (88.9)	0	0	17 (13.2)	13 (16.7)
2	3 (10)	1 (5.6)	0	0	11 (8.5)	5 (6.4)
3	0	1 (5.6)	6 (20)	4 (20)	42 (32.6)	24 (30.8)
4	0	0	23 (76.7)	16 (80)	34 (26.4)	26 (33.3)
5	0	0	1 (3.3)	0	22 (17.1)	8 (10.3)
6	0	0	0	0	3 (2.3)	2 (2.6)
Duration of surgery, median (range), min						
	146 (55-320)	180.5 (63-239)	46 (28-120)	46 (27-96)	168 (77-406)	164.5 (58-399)

SD, standard deviation.
[a]Cohort 1, laparotomy. Cohort 2, laparoscopic cholecystectomy. Cohort 3, laparoscopically assisted colectomy.

Efficacy Outcomes

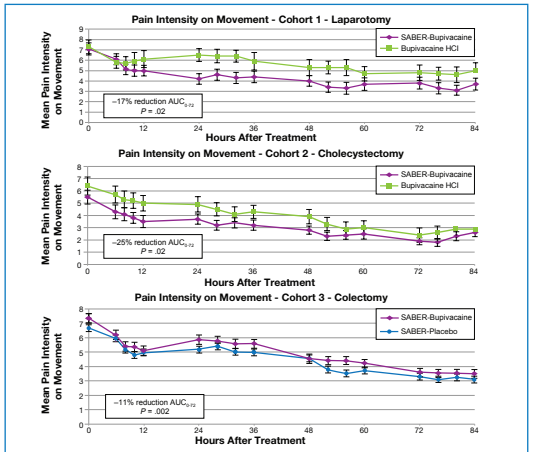
- Prespecified sensitivity analysis of pain intensity using only the scheduled (LogPad) pain scores and excluding the opioid rescue pain scores was performed to assess the therapeutic effect of SABER-Bupivacaine without the complication of frequent opioid pain rescue scores that, unlike the scheduled scores, might not have reflected incisional pain (inferential analysis with ANOVA)[6] (**Figure 1**)

Figure 1. Pain intensity on movement (excluding opioid concomitant medication pain scores) were improved across combined cohorts 1 and 2 and cohort 3 (ITT population).



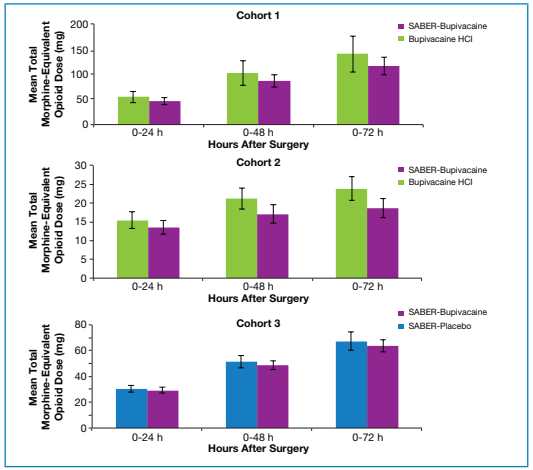
- Repeated-measures analysis at each scheduled pain assessment was used to partition variability resulting from individual patient differences, given the relatively short period of observation and the low attrition rate. All cohorts showed statistically significant therapeutic effects during the 0- to 72-hour observation period in the repeated-measures analysis[6] (**Figure 2**)

Figure 2. Repeated-measures pain intensity on movement during the 0- to 72-hour period (ITT population).



- Wide variations in opioid use were observed between patients, and the data were skewed. Mean opioid use was lower in the SABER-Bupivacaine group than in the control group, but this difference was not statistically significant[6] (**Figure 3**)

Figure 3. Total morphine-equivalent opioid medication dose (ITT population).



Safety

- Cardiovascular and neurologic treatment-emergent AEs (TEAEs) were of special interest because high plasma concentrations of bupivacaine may cause AEs in these body systems[6]
  - The Holter data showed no consistent treatment-related effects on any of the ECG intervals, including QTcF
  - No consistent imbalances between treatment groups and no evidence of bupivacaine toxicity were observed (**Table 2**)
- Overall, AEs were similar between SABER-bupivacaine and control groups, and there were no reports of bupivacaine toxicity[6] (**Table 2**)

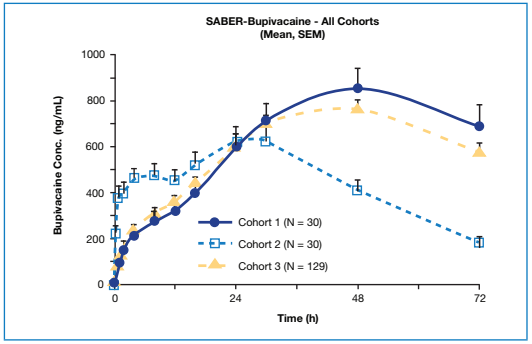
Table 2. Summary of TEAEs

n (%)	Cohort 1[a]		Cohort 2[a]		Cohort 3[a]	
	SABER-Bupivacaine n = 30	Bupivacaine HCl n = 18	SABER-Bupivacaine n = 30	Bupivacaine HCl n = 20	SABER-Bupivacaine n = 129	SABER-Placebo n = 78
≥1 TEAE	30 (100)	17 (94)	28 (93)	20 (100)	126 (98)	75 (96)
≥1 cardiovascular TEAE	4 (13)	7 (39)	2 (7)	2 (10)	19 (15)	6 (8)
≥1 neurologic TEAE	6 (20)	4 (22)	17 (57)	10 (50)	23 (18)	29 (37)
≥1 serious TEAE	9 (30)	4 (22)	0	1 (5)	16 (12)	9 (12)

Pharmacokinetics

- SABER-Bupivacaine provides immediate, continuous, and effective 72-hour delivery of bupivacaine directly at the surgical site[6]
- Bupivacaine concentrations were well below toxicity level concerns and did not demonstrate a burst effect[6]
- Administration of SABER-Bupivacaine in the 3 cohorts resulted in similar plasma concentration-by-time profiles, except for an earlier T_{max} observed in cohort 2 compared with the other cohorts[6] (**Figure 4**)

Figure 4. Bupivacaine serum concentration.



CONCLUSIONS

- Prespecified sensitivity analyses that excluded opioid rescue pain scores from the analysis yielded more significant results, and repeated-measures analysis of pain intensity on movement from 0 to 72 hours was statistically significant for all 3 cohorts compared with controls
- SABER-Bupivacaine was well tolerated when instilled into a variety of abdominal surgical wounds at a dose of 5 mL (660 mg); there was no evidence of systemic bupivacaine toxicity as assessed by AEs, laboratory testing, and intensive Holter monitoring
- Overall, treatment with SABER-Bupivacaine provided a clinically meaningful reduction in pain intensity over a 72-hour postoperative period compared with either active or placebo controls

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