Treatment of postoperative pain in shoulder surgery with SABER®-Bupivacaine

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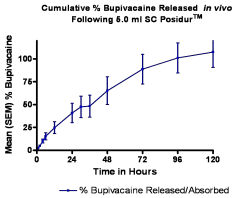
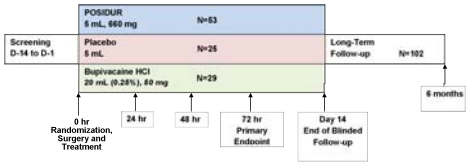
BACKGROUND

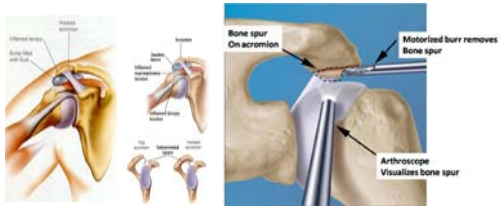
- Local anesthetics are an important component of multimodal postsurgical analgesia, but are limited by a short duration of action (4-8 hours)
- Relief of postsurgical pain with local anesthetics has been shown to reduce the need for opioid treatment, with an attendant reduction in opioid-related adverse events
- For many surgeries, severe to moderate pain lasts for about 3 days
- POSIDUR™ was designed to release bupivacaine over a 3 day period
- The POSIDUR formulation is a free-flowing solution containing 132 mg/mL of bupivacaine base
- The recommended dose of POSIDUR is 5 ml (660 mg) instilled directly into the surgical incisions
- When instilled into a surgical incision prior to closure, the product forms a viscous depot that releases bupivacaine over a 3 day period at a rate of about 10 mg/hour
- The rate of release is well-controlled and there is no evidence of dose dumping



TRIAL DESIGN



SURGICAL PROCEDURE



METHODS

Trial Design: Multinational, randomized, parallel, double-blind, placebo and active controlled

Study Sites: 9 sites in Austria, Denmark, Germany, Latvia, Sweden

Inclusion Criteria: Subacromial impingement syndrome, intact rotator cuff on MRI imaging, ≥ 18 years, male or female (with negative pregnancy test and adequate contraception)

Exclusion Criteria: other shoulder pathology, clinically significant comorbidity, abnormal ECG, QT > 450 msec (M), QR > 470 msec (F), use of drugs contraindicated on bupivacaine label

Study Treatments: POSIDUR (5mL, 660 mg), SABER-Placebo (5 mL), or Bupivacaine HCl (20 mL, 0.25%, 50 mg) were deposited into subacromial space through an arthroscopic portal under direct vision

Background analgesia: Acetaminophen, 1000 mg qid (wt ≥ 66kg) or 500 mg qid (wt < 66kg) for 0-72 hours post-surgery

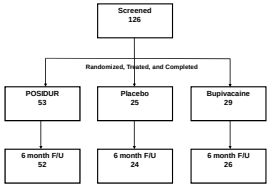
Rescue Analgesia: Morphine 2 mg IV or 10 mg PO as requested for pain relief

Measurements: Pain intensity on shoulder flexion to 90° using 0-10 numerical rating scale at scheduled time points (1, 2, 4, 6, 8, 12 hours post-op, then at 8AM, 12PM, 4PM, 8PM on postoperative days 1-7). Rescue opioid use recorded 4 times/day from 0-72 hours post-op. PK at baseline, 1, 4, 8, 12, 24, 36, 48, 72, 96 hours post-dose. Safety assessments: adverse events, serum chemistry and hematology, surgical wound healing, vital signs, ECG, and MRI at 6 month FU

Endpoints: Pain – time normalized AUC of pain intensity on movement from 1-72 hours (AUC_{1-72}). Opioid use – total opioids used over 0-72 hours post-op converted to IV morphine equivalents (MED_{0-72})

Statistical Analysis: Pain AUC_{1-72} – ANOVA with treatment and pooled sites as factors. Total Opioid use (MED_{0-72}) Wilcoxon rank-sum test.

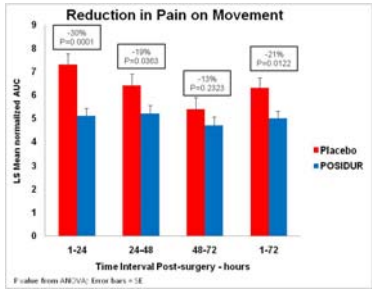
PATIENT DISPOSITION



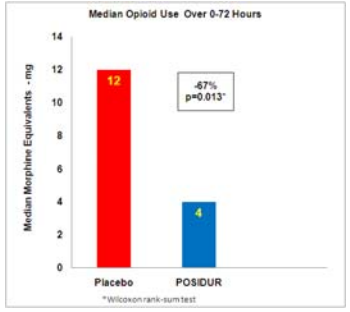
DEMOGRAPHY

Demographics (ITT population)	POSIDUR N=53	Placebo N=25	Bupivacaine N=29	Total N=107
Gender, n (%)				
Female	33 (62.3)	14 (56.0)	17 (58.6)	64 (59.8)
Male	20 (37.7)	11 (44.0)	12 (41.4)	43 (40.2)
Age (years)				
Mean	50.1	48.6	51.6	50.2
Median	49	51	52	51
Min, max	28, 70	24, 63	21, 70	21, 70
Race, n (%)				
Asian	0 (0.0)	1 (4.0)	0 (0.0)	1 (0.9)
Hispanic	2 (3.8)	0 (0.0)	0 (0.0)	2 (1.9)
White	50 (94.3)	24 (96.0)	29 (100)	103 (96.3)
Other	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.9)
BMI - kg/m^2				
Mean	26.77	25.83	26.65	25.52
Median	26.5	25.76	24.45	26.08
Min, max	20.3, 35.3	19.3, 34.5	21.5, 41.5	19.3, 41.5

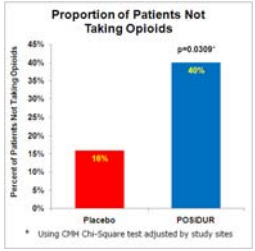
PAIN REDUCTION



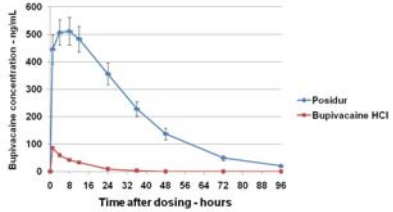
REDUCTION IN OPIOID USE



PATIENTS NOT NEEDING ANY OPIOIDS



PHARMACOKINETICS



SURGICAL WOUND HEALING

Day	Surgical Site Healing	POSIDUR n	POSIDUR (%)	Placebo n	Placebo (%)	Bupivacaine n	Bupivacaine (%)
Day 7	Surgical healing as expected	53	100%	24	96%	29	100%
	Healing Not as expected	0	0	0	0	0	0
Day 14	Surgical healing as expected	53	100%	25	100%	29	100%
	Healing Not as expected	0	0	0	0	0	0
6 month follow-up	Surgical healing as expected	52	98%	25	100%	26	90%
	Healing Not as expected	0	0	0	0	0	0

ADVERSE EVENTS

Primary SOC / Preferred Term	POSIDUR N=53	Placebo N=25	Bupivacaine N=29
All TEAEs	16 (30.2%)	10 (40%)	11 (37.9%)
Nervous system disorders	5 (9.4%)	2 (8%)	4 (13.8%)
Headache	3 (5.7%)	1 (4%)	1 (3.4%)
Investigations	5 (9.4%)	2 (8%)	2 (6.9%)
Alanine aminotransferase increased	1 (1.9%)	2 (8%)	0 (0%)
Gastrointestinal disorders	2 (3.8%)	3 (12%)	1 (3.4%)
Nausea	1 (1.9%)	3 (12%)	1 (3.4%)
Cardiac disorders	1 (1.9%)	2 (8%)	3 (10.3%)
Musculoskeletal and connective tissue disorders	3 (5.7%)	1 (4%)	2 (6.9%)
Musculoskeletal pain	2 (3.8%)	1 (4%)	2 (6.9%)
Skin and subcutaneous tissue disorders	2 (3.8%)	2 (8%)	2 (6.9%)
Injury, poisoning and procedural complications	3 (5.7%)	1 (4%)	0 (0%)
General disorders and administration site conditions	1 (1.9%)	2 (8%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	0 (0%)	2 (6.9%)

CONCLUSIONS

- The trial was well-conducted and no patients dropped out
- POSIDUR treatment resulted in clinically and statistically significant reduction in post-surgical pain compared to placebo
- POSIDUR reduced pain on each of the 3 days following surgery
- POSIDUR significantly reduced the use of opioid rescue medication by 67% compared to placebo
- 40% of POSIDUR patients took no opioids
- POSIDUR was well tolerated and had no adverse effect on wound healing
- There were no adverse effects due to systemic bupivacaine toxicity