2187799

Intra-incisional depot bupivacaine reduces pain intensity and opioid consumption for 72 hours following open laparotomy, compared with bupivacaine HCl

Harry Papaconstantinou[1], Jorge Marcet[2], Dave Ellis[3], Jon Meisner[3], and Afif Hadj[4]

[1]Department of Surgery, Baylor Scott & White Memorial Hospital and Clinic, Temple, TX; [2]Department of Surgery, University of South Florida, Tampa, FL; [3]DURECT Corporation, Cupertino, CA; [4]University of Melbourne, Melbourne, Victoria, Australia

INTRODUCTION

- Despite advances in analgesia, patients often experience significant pain in the 72 hours following surgery[1,2]
- Multimodal pain management strategies combine analgesic agents of different classes and routes of administration with the goals of reducing the consequences of inadequate pain control and limiting adverse effects associated with opioid analgesics[3,4]
- Enhanced recovery protocols that incorporate multimodal analgesia are also evolving to improve pain control, reduce length of postoperative hospital stays, enable earlier return of function, and improve patient outcomes[5,6]
- Intra-incisional depot bupivacaine (IDB)* contains the active ingredient bupivacaine (660 mg in a single 5-mL dose) in a delivery platform composed of a biodegradable organic matrix (sucrose acetate isobutyrate) and the solvent benzyl alcohol
  - IDB is instilled via needle-less syringe directly into the surgical incision prior to closure
  - The solvent diffuses rapidly on instillation, leaving an extended-release depot that delivers local anesthetic to the surgical site throughout the first 72 postoperative hours
- A randomized, double-blind, controlled study was conducted to extend the existing clinical experience with IDB to patients undergoing major abdominal surgery

METHODS

- This Phase 3, multicenter, double-blind, active-controlled study randomized patients undergoing open laparotomy for a variety of non-emergent indications to receive (in a 3:2 ratio) either
  - Study drug: IDB 13.2% (5ml, 660 mg bupivacaine) instilled directly into the incision just prior to closure or
  - Active control: bupivacaine HCl 0.5% (30 mL, 150 mg) infiltrated peri-incisionally at closure
- Efficacy evaluations included postoperative pain intensity, total opioid use, and dischargeability
- Patient-assessed pain intensity upon movement was determined using an 11-point Pain Intensity Numeric Rating Scale (PI-NRS) that ranged from 0 (no pain) to 10 (pain as bad as you can imagine)
  - On the day of surgery (day 0), patients entered their assessments into electronic diaries upon awakening from surgery and at 6, 8, 10, and 12 hours post dose
  - On each postsurgery day from 1 to 7, patients completed an assessment at each of 4 time points (08:00, 12:00, 16:00, and 20:00 hours)
  - A repeated measures mixed-effect model ANCOVA was used to compare pain intensity across treatment groups over the first 3 postsurgical days, with incision length as the covariate
- Mean total intravenous (IV) morphine-equivalent opioid medication use for rescue analgesia was calculated for each group
  - Any patient reporting moderate to severe postoperative pain (PI-NRS score ≥4) could receive opioid rescue analgesia
  - Morphine-equivalent opioid doses were analyzed over the 0 to 24, 0 to 48, and 0 to 72 hour postsurgery time periods using an ANCOVA model with pooled site and treatment group as factors, and incision length as a covariate
- Dischargeability was assessed using the modified Post-Anesthesia Discharge Scoring System (mPADSS) on postoperative days 0, 1, 2, and 7, as well as at the final visit
  - Each of 5 parameters (vital signs, activity level, nausea/vomiting, pain, and surgical bleeding) were evaluated on a 0 to 2 scale; a patient with a total mPADSS score of 9 or 10 was considered eligible for discharge to home care
  - Actual discharge, per study protocol, was delayed to at least 72 hours following surgery regardless of mPADSS score
- Safety parameters included adverse events (AEs), standard blood chemistry and hematology, plasma bupivacaine levels, and electrocardiographic data (72-hour Holter monitor recording)
  - Treatment-emergent adverse events (TEAEs) were defined as AEs that occurred during or after dosing, or existing AEs that worsened during the study

RESULTS

- A total of 48 patients, comprising the safety population, received IDB (n=30) or bupivacaine HCl (n=18) (**Table 1**)
  - Common preoperative diagnoses included colon cancer, diverticulitis, and inflammatory bowel disease
- The intention-to-treat (ITT) population included 26 patients randomized to IDB and 17 randomized to bupivacaine HCl who had ≥1 postsurgical pain intensity record

Table 1. Demographic and Clinical Characteristics – Safety Population

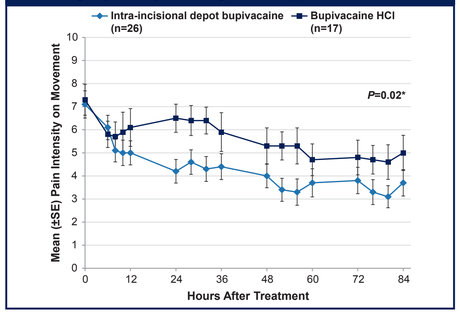
	IDB (n=30)	Bupivacaine HCl (n=18)
Age (years)		
Mean (min, max)	56.8 (28, 85)	53.8 (22, 87)
Gender, n (%)		
Female	12 (40%)	9 (50%)
Male	18 (60%)	9 (50%)
Race, n (%)		
Black or African American	4 (13%)	4 (22%)
White	26 (87%)	14 (78%)
BMI (kg/m^2)		
Mean (min, max)	30.5 (17, 52)	27.0 (20, 36)
Cumulative incision length (cm)		
Mean (min, max)	19.6 (3, 35)	20.7 (6, 32)
Median	20.0	21.0
Number of incisions, n (%)		
1	27 (90%)	16 (89%)
2	3 (10%)	1 (6%)
3	0	1 (6%)
≥4	0	0
Time to hospital discharge (days)		
Median (min, max)*	6.2 (3, 25)	6.6 (4, 14)

*ITT population

EFFICACY ASSESSMENTS

- Repeated measures analysis of the scheduled postoperative pain assessments over the first 72 hours showed a significant reduction in reported pain intensity among patients who received IDB compared with those who received bupivacaine HCl (**Figure 1**)
  - Least squares (LS) mean (± SE) pain on movement from 0 to 72 hours was 4.9 ± 0.30 for the IDB group and 5.9 ± 0.35 for the bupivacaine HCl group (*P*=0.02)

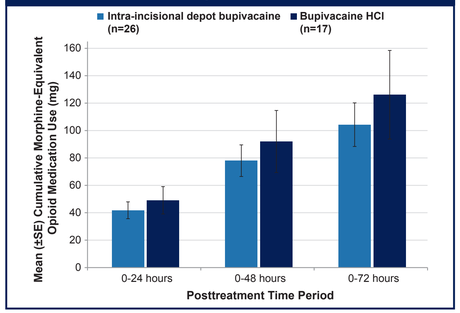
Figure 1. Mean Pain Intensity on Movement Over Time Following Open Laparotomy – ITT Population



*Based on a repeated measures mixed effect ANCOVA model with pooled site and treatment group as fixed factors, incision length as a covariate, patient as a random factor, and time as a repeated measurement factor.

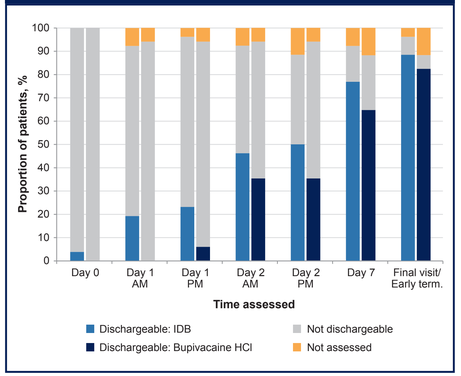
- Over the 72 hours following surgery, patients in the IDB group required a mean ± SE of 104 ± 16 mg morphine equivalents, compared with 126 ± 32 mg for patients in the bupivacaine HCl group (*P*=0.54, based on LS mean difference) (**Figure 2**)

Figure 2. Cumulative Morphine-Equivalent Opioid Medication Dose – ITT Population



- At each time point assessed, the percentage of patients who were considered eligible for discharge was greater in the IDB group than in the bupivacaine group (**Figure 3**), although the differences were not statistically significant

Figure 3. Readiness for Discharge* as Assessed by the modified Post-Anesthesia Discharge Scoring System (mPADSS) – ITT Population



*Patients with an mPADSS score of 9 or 10 were considered eligible for discharge.

SAFETY ASSESSMENTS

- The incidence and severity of reported TEAEs were similar between the IDB and bupivacaine HCl groups (**Table 2**)

Table 2. Summary of Treatment-Emergent Adverse Events – Safety Population

	IDB (n=30) n (%)	Bupivacaine HCl (n=18) n (%)
≥1 TEAE	30 (100)	17 (94)
≥1 cardiovascular TEAE	4 (13)	7 (39)
≥1 neurologic TEAE	6 (20)	4 (22)
≥1 serious TEAE	9 (30)	4 (22)
Maximum severity, all TEAEs		
Mild	5 (17)	2 (11)
Moderate	16 (53)	11 (61)
Severe	9 (30)	4 (22)

CONCLUSIONS

- In this open laparotomy model, IDB significantly reduced postoperative pain intensity for 72 hours compared with bupivacaine HCl
- Opioid consumption was lower in patients treated with IDB compared with bupivacaine HCl, and the proportion of patients judged eligible for discharge was greater at each timepoint assessed, though the differences did not reach statistical significance
- Safety results were comparable for IDB and bupivacaine HCl, with no substantial differences in incidence, type, or severity of TEAEs
- IDB, a novel, sustained-release local analgesic formulation, may prove a useful component of multimodal postoperative pain-management strategies for abdominal surgery

REFERENCES

1. Gan TJ, et al. *Br J Anaesth.* 2004;92(5):681-688.
2. Svensson I, et al. *J Pain Symptom Manage.* 2000;20(3):193-201.
3. Devin CJ, McGirt MJ. *J Clin Neurosci.* 2015 Mar 9. [Epub ahead of print].
4. Fawcett WJ, Baldini G. *Anesthesiol Clin.* 2015;33(1):65-78.
5. Kessler ER, et al. *Pharmacotherapy.* 2013;33(4):383-391.
6. Alvarez MP, et al. *Surg Endosc.* 2014 Dec 6 [Epub ahead of print].

ACKNOWLEDGEMENTS

Funding for editorial support was provided to MedVal Scientific Information Services, LLC (Skillman, NJ), by DURECT Corporation (Cupertino, CA).

*This product is investigational and has not been approved by the FDA.

Presented at the 2015 American Society of Colon and Rectal Surgeons Annual Scientific Meeting • May 30 – June 3, 2015 • Boston, MA