Supplementary Material 1

Anesthesia protocol

As per generally accepted operating procedures, a standardized anesthetic regimen, including general anesthesia with fentanyl (maximum dose of 4 mcg/kg) and propofol (dose at discretion of the anesthesia provider), was included in the trial. Epinephrine, however, was not permitted during the procedure, and no local anesthetics other than XARACOLL in the surgical field or regional anesthesia were permitted either. Lidocaine HCl 1% injection at a dose of no more than 20 mg was allowed to be administered once through intravenous (iv) access to decrease venous irritation at the time of surgical anesthesia. Intraoperative fentanyl was also permitted for analgesia. No other analgesic agents were to be used during the procedure including, but not limited to, opioids (other than fentanyl), acetaminophen (oral or iv), NSAIDs (e.g., ketorolac or COX-2 inhibitors), ketamine, pregabalin, and others. A preoperative dose of an antiemetic, ondansetron iv 4 mg, for nausea prophylaxis was allowed; however, postoperative antiemetic medications were to be given to treat only patients who reported nausea and/or vomiting. Administration of fentanyl was to be avoided 30 minutes prior to the anticipated conclusion of the procedure if medically acceptable in the judgement of the anesthesiologist.

Supplementary Material 2

Rescue Medication protocol

Patients were permitted rescue medication to manage breakthrough pain when it occurred. Oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or oxycodone 5 mg tablet(s) (not to exceed 10 mg in a 4-hour period during the inpatient stay) could be given on an as needed basis for pain. Immediately prior to receiving any rescue medication, a pain intensity score was recorded. If the NPRS score was 4 or less, patients were discouraged from taking opioid rescue medication; however, rescue medication could be requested and provided at any time. If patients required opioid rescue medication, but were unable to take oral medications, they were permitted to receive intravenous morphine (2-3 mg) every 3 hours until they were able to take oral rescue medication. A pain intensity score was collected before any rescue medication use.

Patients with pain intensity scores of 4 or more at discharge were given a written prescription for immediate-release oxycodone at a dosage of 5-10 mg every 4-6 hours as needed as rescue medication for breakthrough pain. Patients prescribed opioid rescue medication were also permitted to take oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4-6 hours as needed for pain, on an outpatient basis. Patients with pain intensity scores of less than 4 at discharge were instructed to take oral acetaminophen at 1000 mg every 4-6 hours (maximum daily dosage 3000 mg) and/or ibuprofen at 400 mg every 4-6 hours as needed for pain, on an outpatient basis. Patients who did not receive a written prescription for oxycodone upon discharge were permitted to request immediate-release oxycodone 5-10 mg if their pain was unrelieved by acetaminophen or NSAIDs. All concomitant medication use during participation in the study was recorded. Following discharge on Day 4, scheduled patient check-ins took place throughout the outpatient postoperative period to monitor recovery. These check-ins occurred on Day 7 (±1 day), 15 (±3 days), and 30 (±3 days); the Day 7 check-in was conducted via telephone, whereas the Day 15 and Day 30 check-ins were conducted in a clinical setting.

Supplementary Material 3

Signs and Symptoms checklist for AEs of special interest

Systemic Bupivacaine Toxicity	**Wound healing**
– Respiratory difficulty	– Purulent discharge or leakage of fluid from site
– Change in level of consciousness	– Pain or soreness
– Restlessness	– Redness or inflammation (edges of wound)
– Anxiety	– Warmth around the wound
– Difficulty speaking or being understood	– Swelling around the wound
– Light-headedness	– Separation of edges of the wound
– Numbness and tingling of mouth and lips	– Seen by health care provider about wound
– Metallic taste	– Prescribed antibiotics for infection of wound
– Tinnitus (ringing in ears)	– Admitted to hospital with infection of wound
– Dizziness	
– Changes in vision	
– Tremors	
– Depression	
– Drowsiness	

Supplementary Material 4

Plasma level concentrations assessed for bupivacaine toxicity

Investigators were instructed to collect blood samples for bupivacaine plasma concentrations if they felt the patient might be experiencing systemic bupivacaine toxicity. In addition, if the patient experienced a **grade 4 AE** (defined as *"life threatening consequences: urgent intervention indicated"*) of any of the following:

- respiratory difficulty
- change in level of consciousness
- cardiovascular event
- 3 or more of the other signs and symptoms on the list concurrently

Eight patients had a blood sample collected, four in each treatment group, at the discretion of the investigator. There were no grade 4 AEs as descripted above and no verbatim reports of systemic bupvicaine toxicity. Bupivacaine plasma concentrations measured (all ≤135 ng/mL) for these patients were well below a level suggestive of systemic bupivacaine toxicity, which is general 2000 ng/mL or more[1,2].

[1] Bardsley, et al., *A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers.* British journal of clinical pharmacology, 1998. 46(3): p. 245-249.

[2] Jorfeldt, et al., *The effect of local anaesthetics on the central circulation and respiration in mand and dog.* Acta Anaesthesiologica Scandinavica, 1968. 12(4): p. 153-169.

Supplementary Material 5

Southampton Wound Grading System

GRADE	APPEARANCE
0	**Normal healing**
I	**Normal healing with mild bruising or erythema**
A	Some bruising
B	Considerable bruising
C	Mild erythema
II	**Erythema plus other signs of inflammation**
A	At one point
B	Around sutures
C	Along wound
D	Around wound
III	**Clear haemoserous discharge**
A	At one point only (≤2cm)
B	Along wound (>2cm)
C	Large volume
D	Prolonged (>3 days)
MAJOR COMPLICATIONS	
IV	**Pus**
A	At one point only (≤2cm)
B	Along wound (>2cm)
V	**Deep or severe wound infection with/without tissue breakdown**
	Haematoma requiring aspiration

Wound (healing) grading using the Southampton Wound Grading System[3] was performed by the investigator (physician) at 72 hours (day 4) posttreatment, day 15, and day 30. Investigator judgment was used to determine if a finding was an adverse event (AE).

The counts and percentages of patients in each category of the Southampton Wound Grading Scale were reported at each time point that it was collected. Results are provided in the table below. On day 4 (prior to discharge), all patients (100%) had wounds graded 0, I, or II. On day

[3] Bailey, et al., *Community surveillance of complications after hernia surgery.* British Medical Journal, 1992. 304(6825): p. 469-471.

15, 85% of patients had wounds graded 0, I, or II; 10% grade III; 2% grade IV; and 0% grade V (3% was not assessed). On day 30, 84% of patients had grade 0, I, or II; 7% grade III, 1% grade IV; and 0% grade V (8% was not assessed).

Summary of Patients with Southampton Wound Grading System Findings by Treatment and Time Point (Safety Population)

Time point	Grade (appearance)	Study treatment		Total (N=365)
		INL-001 (N=181)	Placebo (N=184)	
Day 4 (prior to discharge)	0 (Normal healing)	136 (75.1)	134 (72.8)	270 (74.0)
	I Normal healing with mild bruising or erythema:	42 (23.2)	48 (26.1)	90 (24.7)
	a (some bruising)	22 (12.2)	24 (13.0)	46 (12.6)
	b (considerable bruising)	0	2 (1.1)	2 (0.5)
	c (mild erythema)	20 (11.0)	22 (12.0)	42 (11.5)
	II Erythema plus other signs of inflammation:	2 (1.1)	2 (1.1)	4 (1.1)
	a (at one point)	1 (0.6)	1 (0.5)	2 (0.5)
	b (around sutures)	0	1 (0.5)	1 (0.3)
	c (along wound)	1 (0.6)	0	1 (0.3)
	d (around wound)	0	0	0
	III Clear or haemoserous discharge:	0	0	0
	a (at one point only (≤2 cm))	0	0	0
	b (along wound (>2 cm)	0	0	0
	c (large volume)	0	0	0
	d (prolonged (>3 days))	0	0	0
	Major Complications:			
	IV Pus:	0	0	0
	a (at one point only (≤2 cm))	0	0	0
	b (along wound (>2 cm))	0	0	0
	V Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	0	0	0
	Not assessed	1 (0.6)	0	1 (0.3)
Day 15	0 (Normal healing)	127 (70.2)	129 (70.1)	256 (70.1)
	I Normal healing with mild bruising or erythema:	23 (12.7)	23 (12.5)	46 (12.6)
	a (some bruising)	8 (4.4)	11 (6.0)	19 (5.2)
	b (considerable bruising)	15 (8.3)	12 (6.5)	27 (7.4)
	c (mild erythema)	0	0	0
	II Erythema plus other signs of inflammation:	5 (2.8)	5 (2.7)	10 (2.7)
	a (at one point)	2 (1.1)	3 (1.6)	5 (1.4)
	b (around sutures)	2 (1.1)	0	2 (0.5)
	c (along wound)	1 (0.6)	2 (1.1)	3 (0.8)
	d (around wound)	0	0	0
	III Clear or haemoserous discharge:	19 (10.5)	17 (9.2)	36 (9.9)
	a (at one point only (≤2 cm))	17 (9.4)	16 (8.7)	33 (9.0)
	b (along wound (>2 cm)	2 (1.1)	1 (0.5)	3 (0.8)
	c (large volume)	0	0	0
	d (prolonged (>3 days))	0	0	0
	Major Complications:			
	IV Pus:	3 (1.7)	4 (2.2)	7 (1.9)
	a (at one point only (≤2 cm))	3 (1.7)	4 (2.2)	7 (1.9)
	b (along wound (>2 cm))	0	0	0

Summary of Patients with Southampton Wound Grading System Findings by Treatment and Time Point (Safety Population)

Time point	Grade (appearance)	Study treatment		Total (N=365)
		INL-001 (N=181)	Placebo (N=184)	
	V Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	0	0	0
	Not assessed	4 (2.2)	6 (3.3)	10 (2.7)
Day 30	0 (Normal healing)	134 (74.0)	130 (70.7)	264 (72.3)
	I Normal healing with mild bruising or erythema:	14 (7.7)	12 (6.5)	26 (7.1)
	a (some bruising)	4 (2.2)	1 (0.5)	5 (1.4)
	b (considerable bruising)	10 (5.5)	11 (6.0)	21 (5.8)
	c (mild erythema)	0	0	0
	II Erythema plus other signs of inflammation:	9 (5.0)	6 (3.3)	15 (4.1)
	a (at one point)	3 (1.7)	1 (0.5)	4 (1.1)
	b (around sutures)	1 (0.6)	1 (0.5)	2 (0.5)
	c (along wound)	4 (2.2)	4 (2.2)	8 (2.2)
	d (around wound)	1 (0.6)	0	1 (0.3)
	III Clear or haemoserous discharge:	16 (8.8)	10 (5.4)	26 (7.1)
	a (at one point only (≤2 cm))	15 (8.3)	9 (4.9)	24 (6.6)
	b (along wound (>2 cm)	1 (0.6)	1 (0.5)	2 (0.5)
	c (large volume)	0	0	0
	d (prolonged (>3 days))	0	0	0
	Major Complications:			
	IV Pus:	1 (0.6)	4 (2.2)	5 (1.4)
	a (at one point only (≤2 cm))	1 (0.6)	4 (2.2)	5 (1.4)
	b (along wound (>2 cm))	0	0	0
	V Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	0	0	0
	Not assessed	7 (3.9)	22 (12.0)	29 (7.9)

Supplementary Material 6

Additional SPI outcomes

		INL-001	Placebo	INL-001 vs Placebo LS Mean Difference (95%CI)[a]	p-value
SPI2	Mean(SD)	9.68 (3.233)	10.51 (2.836)		
	95%CI	9.24 - 10.13	10.06 - 10.94	-0.82 (-1.44 - -0.19)	0.01
SPI3	Mean(SD)	16.2 (5.3)	17.85 (4.584)		
	95%CI	15.5-17.0	17.12 - 18.55	-1.6 (-2.61 - -0.58)	0.002
SPI4	Mean(SD)	22.4 (7.5)	24.8 (6.5)		
	95%CI	21.4-23.4	23.8-25.8	-2.45 (-3.88 - -1.01)	0.001
SPI5	Mean(SD)	28.1 (9.6)	31.6 (8.6)		
	95%CI	26.8-29.5	30.2-32.8	-3.36 (-5.22 - -1.50)	<0.001
SPI6	Mean(SD)	33.1 (11.4)	37.5 (10.4)		
	95%CI	31.6-34.7	35.9-39.1	-4.38 (-6.61 - -2.15)	<0.001
SPI8	Mean(SD)	41.3 (14.7)	47.8 (14.0)		
	95%CI	39.3-43.5	45.7-49.8	-6.4 (-9.33 - -3.47)	<0.001
SPI10	Mean(SD)	48.9 (18.2)	57.3 (17.7)		
	95%CI	46.3-51.5	54.7-59.9	-8.37 (-12.05 - -4.69)	<0.001
SPI12	Mean(SD)	56.4 (21.8)	66.5 (21.5)		
	95%CI	53.2-59.6	63.4-69.6	-10.09 (-14.54 - -5.65)	<0.001
SPI18	Mean(SD)	79.4 (32.2)	92.41 (32.873)		
	95%CI	74.7-84.2	87.64 - 97.06	-12.91 (-19.60 - -6.22)	<0.001
SPI20	Mean(SD)	81.7-92.3	100.41 (36.870)		
	95%CI	86.9 (35.7)	95.09 - 105.61	-13.38 (-20.85 - -5.92)	<0.001
SPI24	Mean(SD)	102.1 (42.9)	117.0 (45.2)		
	95%CI	95.7 – 108.6	110.5 – 123.3	−14.8 (−23.8, −5.7)	0.001
SPI28	Mean(SD)	117.21 (50.092)	133.10 (53.465)		
	95%CI	109.71 - 124.85	125.52 - 140.53	-15.74 (-26.40 - -5.08)	0.004
SPI32	Mean(SD)	132.49 (57.540)	148.82 (61.761)		
	95%CI	123.85 - 141.30	140.09 - 157.39	-16.16 (-28.45 - -3.88)	0.01
SPI36	Mean(SD)	147.88 (65.329)	163.70 (69.828)		
	95%CI	138.10 - 157.86	153.81 - 173.41	-15.63 (-29.54 - -1.71)	0.028
SPI48	Mean(SD)	190.4 (87.7)	205.8 (95.9)		
	95%CI	177.1 – 204.0	192.4 – 219.0	−15.2 (−34.1, 3.7)	0.12
SPI72	Mean(SD)	264.60 (131.35)	281.10 (146.28)		
	95%CI	244.4 – 285.1	260.8 – 301.1	−16.2 (−44.8, -12.5)	NA[b]

[a] Least Squares Mean Difference (95% Confidence Interval) based on ANCOVA model with Body Mass Index as covariate
[b] Because of the multiplicity algorithm, all secondary variables tested after SPI48 were declared not statistically significant