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**Intraperitoneal instillation of local anaesthetic (IPILA) in bariatric surgery and the effect on post-operative pain scores: A randomised control trial**

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# Intraperitoneal instillation of local anaesthetic (IPILA) in bariatric surgery and the effect on post-operative pain scores: A randomised control trial



A thesis submitted to The University of Notre Dame Australia to satisfy the partial requirements of the Masters of Medicine/Masters of Surgery

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## **List of publications**

Peer reviewed journal article

Kaur R, Seal A, Lemech I, Fisher O, Williams N. Intraperitoneal instillation of local anaesthetic (IPILA) in bariatric surgery and the effect on post-operative pain scores: A randomized control trial. *Obes Surg*, 2022, 10.1007/s11695-022-06086-w

Conference presentation

Kaur R, Seal A, Lemech I, Williams N. Intraperitoneal instillation of local anaesthetic (IPILA) in bariatric surgery: A randomized control trial. IFSO 25<sup>th</sup> World Congress, Miami, Florida, USA. (Delayed to 2022 due to COVID)

This research has undergone rigorous peer-review and has been published as indicated above. For the purposes of the thesis, additional context has been added in Chapter one and an expanded discussion has been added in Chapter three.

## **Declaration**

I declare that this thesis is composed of entirely my own original research and contains content which had not been previously submitted for an award or degree or diploma in any institution. There is no material in this thesis which has been previously written or published by another individual except where due reference has been made in the text. The contributions of others to this thesis have been acknowledged and stated clearly. No conflicts of interest have been identified.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, updated 2018). The proposed research study received human research ethics approval from the University of Notre Dame Australia Human Research Ethics Committee (EC00418), Approval Number # 018114S. The proposed research study was also registered with the Australia and New Zealand Clinical Trials Registry, Approval number ACTRN 12618000389202.

## **Acknowledgements**

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I wish to acknowledge the efforts of Dr Oliver Fisher for assisting us in our data analysis and also of all of the staff who have assisted in data collection and patient care, particularly the nursing staff, who were vital to the success of this project.

Finally, to the wonderful patients who chose to partake in this project and dedicate time and efforts throughout their healthcare journey. Without their participation, advances in clinical sciences would not be possible.

## Preface

The rise of obesity in our population has increased demand for bariatric surgery. This has emphasised the need to optimise post-operative care in this high-risk population to reduce complications and length of stay (LOS). The idea for this study and thesis was prompted from observations in clinical practice; that the two primary factors contributing to prolonged LOS were pain and nausea. Increased pain restricts patient movement and normalisation of function, commonly requiring higher doses of opioid analgesia. This is also associated with worsening side effects such as constipation, drowsiness and nausea. Nausea of any cause post-operatively also restricts oral intake and mobility, contributing to longer inpatient stays. Nevertheless, it was observed that patients most often complained of “gas pain” secondary to pneumoperitoneum and diaphragmatic irritation, which is often poorly responsive to opioid analgesia. The focus of this study was to investigate whether instillation of intraperitoneal anaesthetic would reduce diaphragmatic irritation and referred shoulder tip pain, which is most commonly experienced post-operatively, whilst reducing opioid requirements and their associated side effects. In order to standardise analgesic effects in this diverse patient population, a weight-based approach was utilised to select the volume of local anaesthetic used, avoiding toxic dosing or under dosing in lighter or heavier patients respectively.

This thesis is divided into three chapters which detail the background of the study, the study itself, and an extended discussion of the outcomes. Chapter one introduces core ideas of the research and provides a literature review exploring rationale behind this study’s design. Chapter two presents the methods and results sections of the paper as published in *Obesity Surgery* (<https://link.springer.com/article/10.1007/s11695-022-06086-w>). Finally, chapter 3 compares this study to similar research and discusses its relevance and importance alongside conclusions drawn.

## Abstract

### Background

Effective analgesia during bariatric procedures may be vital as it could reduce post-operative opioid use. This can lead to less nausea which may be associated with shorter post-operative length of stay (LOS). Understanding analgesic requirements in patients with obesity is important due to the varied physiology and increased number of comorbidities.

### Objectives

The aim of this study was to evaluate the efficacy of IntraPeritoneal Instillation of Local Anaesthetic (IPILA) to reduce opioid requirements in patients undergoing laparoscopic bariatric surgery.

### Methods

A double-blinded randomised control trial was conducted to compare intraperitoneal instillation of ropivacaine to normal saline in 104 patients undergoing bariatric surgery. The primary endpoint was pain in recovery with secondary endpoints at 1, 2, 4, 6, 24 and 48 hrs post-operatively. Further endpoints were post-operative analgesic use and LOS. Safety endpoints included unexpected reoperation or readmission, complications and mortality.

### Results

There were 54 patients in the placebo arm and 50 in IPILA. Pain scores were significantly lower in the IPILA group both at rest ( $p=0.04$ ) and on movement ( $p=0.02$ ) in recovery with no difference seen at subsequent time points. Equally, IPILA was independently associated with reducing severe postoperative pain at rest and movement (adjusted odds ratio [aOR] 0.28, 95%CI 0.11-0.69,  $p=0.007$  and aOR 0.25, 95%CI 0.09-0.62,  $p=0.004$ , respectively). There was no significant difference in LOS, opioid use, antiemetic use, morbidity or mortality between the intervention and placebo groups.



## Conclusion

The administration of ropivacaine intraperitoneally during laparoscopic bariatric surgery reduces post-operative pain in the recovery room but does not reduce opioid use nor LOS.

## Key Words

Bariatric surgery, intraperitoneal instillation, ropivacaine, post-operative pain

## Key Points

- Intraperitoneal local anaesthetic reduces severe post-operative pain in the recovery room
- There is no change in post-operative pain beyond 1 hour
- There is no change in overall use of opioids nor length of stay

## Chapter 1: Extended Introduction

Obesity is a chronic disease, with incidence rising annually around the globe [1]. It is associated with a reduced life expectancy through the development of related conditions including cardiovascular disease, diabetes and certain cancers [1]. Bariatric surgery is the most effective treatment for obesity, especially if used in combination with other treatments such as dietary/lifestyle modification, pharmacotherapy and psychotherapy [2-4]. With the increased focus on enhanced recovery after surgery (ERAS), length of stay (LOS) of bariatric surgery has been significantly reduced. There is also growing interest in the option of day-stay bariatric surgery, and so increasing efforts are being made to optimise post-operative management of these patients.

The primary barriers to reduction in LOS are post-operative pain and nausea. The pain produced by laparoscopic procedures usually manifests as referred shoulder tip pain and is associated with pneumoperitoneum and diaphragmatic irritation. There are two main stimuli which contribute to this: visceral pain from the operative site and nociceptive pain due to abdominal wall stimulation, decreased intra-abdominal pH and/or gas retention at the conclusion of a procedure [5]. To combat post-operative pain, opioid analgesia is commonly used. However, use of opioid analgesia does not directly target many of these pathologies and has a range of adverse effects, often exacerbated by the physiology of the obese patient. Opioids are associated with nausea, sedation and opioid-induced ventilatory impairment which can lead to a delay in oral intake, apnoeic episodes and respiratory depression [6-8]. Patients with obesity experience a higher rate of respiratory and cardiovascular complications in the peri-operative and post-operative period including obstructive sleep apnoea, respiratory depression, hypoxia, deep venous thrombosis (DVT), pulmonary embolus (PE) and myocardial infarction [9]. Increasing use of opioid analgesia places bariatric surgical patients at higher risk of complications and increased LOS. Hence, alternative types of analgesia should be explored such as intraperitoneal local anaesthetic.

Several intraperitoneal anaesthetic techniques have been developed and evaluated including intra-peritoneal local anaesthetic (IPILA), peri-portal infiltration [6,10] or

aerosolisation [7,8]. The safety and efficacy of local anaesthetic in perioperative care is well recognised. The primary advantages of local anaesthetic agents are that they act predominantly on the tissue to which they are administered, and they comparatively lack the systemic effects of opioids. When selecting the type of local anaesthetic to use intraperitoneally, two main drugs were considered. Bupivacaine and ropivacaine are the primary intraperitoneal local anaesthetic drugs used in most studies. Both drugs reduce post-operative pain when used intraperitoneally [11-16]. In one study, treatment groups received varied doses of intraperitoneal ropivacaine with 50mg, 100mg and 150mg. There was no difference in mean pain intensity, length of hospital stay nor readiness for discharge between the groups [17]. Another study comparing both drugs reported that ropivacaine was more effective after the 7<sup>th</sup> hour post-operatively than bupivacaine [18]. Of the two drugs ropivacaine is less lipophilic, and therefore less likely to penetrate large myelinated motor fibres causing less motor blockade. This was considered important as the anaesthetic would be used around the diaphragm. Ropivacaine is also less neurotoxic and cardiotoxic than bupivacaine [19], and thus was the preferred local anaesthetic agent used in this study.

Results from research conducted on the effectiveness of intraperitoneal local anaesthetic in a range of laparoscopic procedures including bariatric surgery are discordant [10-12, 17, 20-28]. Some demonstrated a reduction in post-operative pain [11, 20, 22-25, 27-28] yet others found no difference [12, 17, 21, 26]. A literature review by Gurusamy *et al.* [21] also confirms this. The studies included in this review were stated to be low to very low quality and the evidence to support intraperitoneal analgesia reducing pain after laparoscopic cholecystectomy was weak. The review concluded that further randomised control trials (RCTs) are necessary, and they should include important clinical outcomes such as quality of life. In contrast, results from a systematic review and meta-analysis by Kahokehr *et al.* [20] that was restricted to RCTs provided evidence that largely supported the use of intraperitoneal instillation of local anaesthetic during laparoscopic cholecystectomies. Kahokehr *et al.* [20] concluded that no further research was required as it would not change the homogeneity of the current evidence. Similarly discordant results are seen in bariatric-specific procedures. The papers that have specifically addressed bariatric surgery will be discussed in chapter 3 of this thesis.

The aim of this study was to evaluate the efficacy of IPILA in patients undergoing laparoscopic bariatric surgery and determine whether it can reduce post-operative pain measures and LOS.

## **Chapter 2: Methods and results sections of publication as seen in Obesity Surgery**

### **Methods**

This was a randomised control trial which was registered with ANZCTR (ACTRN 12618000389202) and was approved by both Calvary Hospital Wagga Wagga administration and the University of Notre Dame Australia Human Research Ethics Committee (Reference number: 018114S). The full trial protocol can be accessed on [www.anzctr.org.au](http://www.anzctr.org.au). Written informed consent was obtained from all participants. Study sample size has been calculated using a standardised effect size of 0.6 using the Cohen's d test and evidence from previous studies [17, 22-24, 27]. The constant used was 0.79 based on  $p < 0.05$  and a power of 80%. A sample size of 100 patients was calculated with 50 in each arm. 20% oversampling was performed to account for missing pain score and follow-up data.

### *Participants*

Adult patients undergoing laparoscopic bariatric surgery [sleeve gastrectomy (SG), one anastomosis gastric bypass (OAGB), Roux-en-Y gastric bypass (RYGB), single anastomosis duodenal-ileal bypass (SADI) and revision surgery] were identified and recruited between November 2018 and November 2020. Patients were excluded if they had an allergy to local anaesthetic, severe cardiovascular disease (congestive heart failure or ischaemic heart disease), chronic renal disease (creatinine clearance  $< 60\text{mL/h}$ ), Child-Pugh Score B/C or if they declined to participate.

### *Surgery*

All patients underwent their procedure with the same surgeon and anaesthetist at a single institution. Laparoscopic procedures were typically carried out using a 12mm optical entry camera port, two 12–15mm operating ports, a 5mm Nathanson liver retractor port and a 5mm assistant port. Carbon dioxide insufflation was set to a pressure of 14mmHg. At the end of each case, a mixing cannula was used to spray a solution of either normal saline or 0.2% ropivacaine onto the diaphragm prior to the conclusion of the procedure. The amount of solution to be instilled was 0.5ml/kg calculated based on the patient weight on the morning of the procedure to ensure safety and efficacy of the local anaesthetic.

### *Anaesthetic protocol*

Patients were given a relaxant general anaesthetic. Standardised monitoring, including 3-lead electrocardiogram, non-invasive blood pressure (NIBP), oxygen saturation and neuromuscular monitoring was attached. Invasive arterial monitoring was used only in the case of poorly fitting or grossly inaccurate NIBP. Patients were positioned in reverse Trendelenburg. Induction proceeded with fentanyl, ketamine, propofol and rocuronium. An endotracheal tube was introduced once deep muscle relaxation was confirmed. The stomach was decompressed with a temporary orogastric tube. Anaesthesia was maintained with oxygen/air/sevoflurane with FiO<sub>2</sub> of 40%. During the case, the patient was converted over to a combination intravenous propofol/Desflurane maintenance with the view to facilitating early respiration and quicker extubation. Each patient received dexamethasone (8mg) at the beginning of the case, unless they were diabetic on oral hypoglycaemic agents or insulin. Parecoxib (40mg), droperidol (0.625mg) and ondansetron (4mg) were administered at the conclusion of the case. Paracetamol (2g) was given on arrival in the post-anaesthesia care unit (PACU) and there was as necessary (PRN) use of antiemetics and oxycodone, or fentanyl if there were allergies as required. All patients received standardised therapy on the ward which was recorded and consisted of PRN ondansetron 4mg QID and Tapentadol 50mg PRN q3h (maximum dose 300mg) and Tramadol 50mg–100mg IV/PO PRN QID. Patients were monitored in a ward-based setting with continuous saturation monitoring. A summary of anaesthetic data is provided in Supplementary Table 1.

### *Randomisation and blinding*

Participants were randomised using block permutation method in a 1:1 ratio between the control and intervention arms. All individuals involved in the trial (patients, surgeons, nurses, and anaesthetists) were blinded to treatment allocation. A member of the research team who was not directly involved in any aspect of the intervention and procedure was unblinded and responsible for randomisation, preparation of solutions and collection of survey forms. The allocation sequence was implemented using sequentially numbered solution bags.

### *Outcome measures*

Pain scores were recorded by nursing staff using a visual analogue scale (VAS) at rest and on movement in the post-operative Acute Care Unit (PACU) and at 1, 2, 4, 6, 24 and 48 hrs. Pain scores at 48hrs were not recorded if the patient had been discharged. The primary endpoint was post-operative pain using VAS score in recovery both at rest and upon movement. Equally, the effect of IPILA on extremes of pain (VAS>7) in PACU were assessed. Secondary endpoints included assessment of pain scores at subsequent time-points until discharge. Other secondary efficacy endpoints were post-operative analgesia and antiemetic use and LOS. Safety endpoints were unexpected reoperation or readmission, complications and mortality.

### *Statistical analysis*

Continuous data for primary and secondary endpoints are summarised as medians with interquartile range or means with 95% confidence intervals (CI) depending on their baseline normal distribution. The primary endpoint of pain scores between treatment and control groups was analysed using Wilcoxon-Rank Sum Test and/or Chi-squared test as required. Secondary endpoints were analysed using Student's independent T-test or non-parametric alternative (Mann-Whitney test) and Pearson chi-square test as appropriate. Fisher's exact test was used for safety endpoints such as reoperation or readmission, complications and mortality due to the low number of events recorded. Uni- and multivariable linear and logistic regression analyses were performed to assess for the independent effect of IPILA on recorded post-operative pain perception. Results included unadjusted (univariable) and adjusted (multivariable) odds ratio with 95% CI estimates. Potential confounders such as surgery type, hiatus hernia repair, age, BMI and chronic pain were controlled for in regression analyses. Data analysis was conducted using SPSS version 20 (Chicago, IL, USA) and R Statistical Programming.

## Results

Of the 120 patients who were randomised, 104 were included in the final analysis, 54 in the placebo arm and 50 in the treatment arm (Figure 1). Baseline demographics did not differ significantly between the two groups (Table 1). Majority of patients underwent SG in both groups. Five patients in each of the placebo and IPILA groups had been prescribed regular analgesic medications for pre-operative chronic pain management. The three revision procedures in the placebo group were all RYGB. In the IPILA group revision procedures were three RYGB, an OAGB and a SADI.

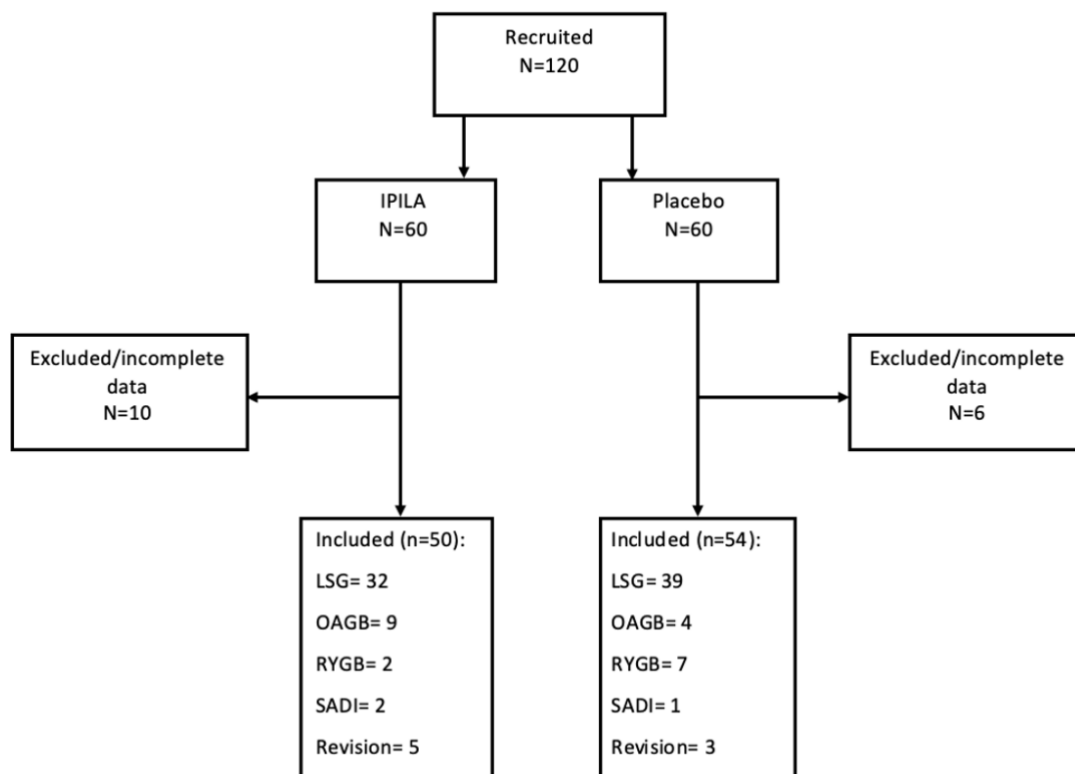


Figure 1: Recruitment and allocation flow diagram

IPILA: intraperitoneal instillation of local anaesthetic

LSG: laparoscopic sleeve gastrectomy

OAGB: one anastomosis gastric bypass

RYGB: Roux-en-Y gastric bypass

SADI: Single anastomosis duodenal ileal bypass



Table 1: Baseline characteristics of patients in the placebo and treatment (IPILA) groups

	<b>Total (N=104)</b>	<b>IPILA (N=50)</b>	<b>Placebo (N=54)</b>	<b>p-value</b>
<b>Patient gender [n(%)]</b>				0.782
<b>Female</b>	82 (78.8)	40 (80.0)	42 (77.8)	
<b>Male</b>	22 (21.2)	10 (20.0)	12 (22.2)	
<b>Patient age (years) median(IQR)</b>	41.0 (29.8–50.0)	44.0 (30.3–49.8)	34.0 (28.0–49.0)	0.099
<b>Patient weight, (kg) median(IQR)</b>	115.8 (101.6–131.5)	117.9 (106.0–131.6)	111.6 (101.4–130.7)	0.540
<b>Body mass index (kg/m2), median (IQR)</b>	40.9 (36.8–46.1)	42.5 (36.8–46.5)	39.3 (36.7–44.9)	0.388
<b>ASA, median (IQR)</b>	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.889
<b>Ethnicity [n(%)]</b>				0.229
<b>ATSI</b>	10 (9.6)	3 (6.0)	7 (13.0)	
<b>Caucasian</b>	94 (90.4)	47 (94.0)	47 (87.0)	
<b>Non-smoker [n(%)]</b>	104 (100.0)	50 (100.0)	54 (100.0)	0.695
<b>Preoperative chronic pain [n(%)]</b>	11 (10.6)	6 (12.0)	5 (9.3)	0.650
<b>Preoperative pain medication use [n(%)]</b>	12 (11.5)	6 (12.0)	6 (11.1)	0.887

<b>Preoperative opioid use [n(%)]</b>	6 (5.8)	4 (8.0)	2 (3.7)	0.348
<b>Preoperative non-opioid use [n(%)]</b>	9 (8.7)	5 (10.0)	4 (7.4)	0.638
<b>Surgery type [n(%)]</b>				0.204
<b>LSG</b>	73 (70.2)	33 (66.0)	40 (74.1)	
<b>OAGB</b>	13 (12.5)	9 (18.0)	4 (7.4)	
<b>RYGB</b>	14 (13.5)	5 (10.0)	9 (16.7)	
<b>SADI</b>	4 (3.8)	3 (6.0)	1 (1.9)	
<b>Revision surgery [n(%)]</b>	8 (7.7)	5 (10.0)	3 (5.6)	0.395
<b>Concomitant hiatus hernia repair [n(%)]</b>	26 (25.2)	17 (34.7)	9 (16.7)	0.035
<b>Length of stay (days) median (IQR)</b>	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.631

ATSI: Aboriginal/Torres Strait Islander

IPILA: Intraperitoneal instillation of local anaesthetic

IQR: interquartile range

LSG: laparoscopic sleeve gastrectomy

OAGB: one anastomosis gastric bypass

RYGB: Roux-en-Y gastric bypass

SADI: Single anastomosis duodenal ileal bypass

Table 2: Median visual analogue scale (VAS) for IPILA and placebo groups post-bariatric surgery and proportion of patients with extreme pain (VAS  $\geq 7$ )

Time point	Action	Median VAS (95% confidence interval)			<i>p</i> -value
		Total	IPILA	Placebo	
<b>PACU</b>	Resting	5.0 (3.0–7.0)	5.0 (3.0–6.0)	6.0 (5.0–8.0)	0.04
	Movement	6.0 (3.0–8.0)	5.0 (3.0–7.0)	7.0 (5.0–8.0)	0.02
<b>PACU n(%)</b>	Resting VAS <7	67 (64.4%)	39 (78.0%)	28 (51.9%)	0.005
	Resting VAS $\geq 7$	37 (35.6%)	11 (22.0%)	26 (48.1%)	
<b>PACU n(%)</b>	Movement VAS <7	58 (56.3%)	36 (72.0%)	22 (41.5%)	0.002
	Movement VAS $\geq 7$	45 (43.7%)	14 (28.0%)	31 (58.5%)	
<b>1 hour</b>	Resting	4.0 (2.0–6.0)	3.0 (2.0–5.8)	4.0 (2.0–6.0)	0.98
	Movement	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.74
<b>2 hours</b>	Resting	3.0 (1.3–5.0)	3.0 (2.0–5.0)	4.0 (1.0–5.0)	0.76
	Movement	4.0 (2.0–5.0)	4.0 (2.5–5.0)	4.0 (2.0–6.0)	0.71
<b>4 hours</b>	Resting	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.5 (1.0–4.0)	0.99
	Movement	3.0 (2.0–6.0)	3.0 (2.0–5.0)	3.0 (2.0–6.0)	0.78
<b>6 hours</b>	Resting	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (2.0–3.5)	0.93
	Movement	4.0 (2.0–5.0)	3.0 (2.0–5.0)	4.0 (2.5–5.0)	0.31
<b>24 hours</b>	Resting	2.0 (1.0–4.0)	2.0 (0.8–3.0)	2.0 (1.0–4.3)	0.23
	Movement	3.0 (2.0–5.0)	3.0 (2.0–4.0)	4.0 (2.0–5.0)	0.52

<b>48 hours</b>	Resting	2.0 (1.0–2.0)	2.0 (0.0–2.0)	2.0 (1.0–2.0)	0.61
	Movement	3.5 (2.0–5.0)	3.0 (2.0–5.0)	4.0 (2.0–5.0)	0.73

PACU: Post-operative acute care unit

IPILA: Intraperitoneal instillation of local anaesthetic

VAS: visual analogue scale

Table 3: Uni- and multivariable regression analyses of factors contributing to reduced extremes of pain as measured in Post-operative Acute Care Unit (PACU) at rest

		Univariable				Multivariable	
		VAS <7	VAS ≥7	aOR (95%CI)	p-value	aOR (95%CI)	p-value
<b>IPILA n(%)</b>	No	28 (41.8)	26 (70.3)	Ref.	-	Ref.	-
	Yes	39 (58.2)	11 (29.7)	0.30 (0.13-0.70)	0.006	0.28 (0.11-0.69)	0.007
<b>Surgery type n(%)</b>	LSG	47 (70.1)	26 (70.3)	Ref.	-	Ref.	-
	OAGB	8 (11.9)	5 (13.5)	1.13 (0.31-3.75)	0.844	1.49 (0.37-5.62)	0.561
	RYGB	9 (13.4)	5 (13.5)	1.00 (0.28-3.23)	0.994	0.94 (0.23-3.55)	0.922
	SADI	3 (4.5)	1 (2.7)	0.60 (0.03-4.98)	0.668	0.66 (0.03-6.64)	0.747
<b>Hiatus hernia repair n(%)</b>	No	48 (72.7)	29 (78.4)	Ref.	-	Ref.	-
	Yes	18 (27.3)	8 (21.6)	0.74 (0.27-1.86)	0.527	1.11 (0.36-3.33)	0.858
<b>Age, mean (SD)</b>		40.6 (12.3)	38.8(12.0)	0.99 (0.95-1.02)	0.463	0.99 (0.95-1.04)	0.797
<b>BMI, mean (SD)</b>		41.4 (6.5)	42.2 (6.6)	1.02 (0.96-1.08)	0.555	1.04 (0.97-1.12)	0.322
<b>Chronic pain n(%)</b>	No	60 (89.6)	33 (89.2)	Ref.	-	Ref.	-
	Yes	7 (10.4)	4 (10.8)	1.04 (0.26-3.70)	0.954	1.16 (0.24-5.29)	0.845

IPILA Intraperitoneal instillation of local anaesthetic

VAS: visual analogue scale

aOR: adjusted odds ratio

CI: confidence interval

SD: standard deviation

BMI: body mass index

LSG: laparoscopic sleeve gastrectomy

OAGB: one anastomosis gastric bypass

RYGB: Roux-en- Y gastric bypass

SADI: Single anastomosis duodenal ileal bypass

Ref: reference category

Table 4: Uni- and multivariable regression analyses of factors contributing to reduced extremes of pain as measured in Post-operative Acute Care Unit (PACU) on movement

				Univariable		Multivariable	
		VAS <7	VAS ≥7	aOR (95%CI)	p-value	aOR (95%CI)	p-value
<b>IPILA n(%)</b>	No	22 (37.9)	31 (68.9)	Ref.	-	Ref.	-
	Yes	36 (62.1)	14 (31.1)	0.28 (0.12-0.62)	0.002	0.25 (0.09-0.62)	0.004
<b>Surgery type n(%)</b>	LSG	40 (69.0)	32 (71.1)	Ref.	-	Ref.	-
	OAGB	6 (10.3)	7 (15.6)	1.46 (0.44-4.95)	0.533	2.58 (0.69-10.20)	0.162
	RYGB	9 (15.5)	5 (11.1)	0.69 (0.20-2.22)	0.547	0.93 (0.22-3.83)	0.925
	SADI	3 (5.2)	1 (2.2)	0.42 (0.02-3.43)	0.458	0.32 (0.01-3.58)	0.389
<b>Hiatus hernia Repair n(%)</b>	No	40 (70.2)	36 (80.0)	Ref.	-	Ref.	-
	Yes	17 (29.8)	9 (20.0)	0.59 (0.23-1.46)	0.261	1.35 (0.44-4.22)	0.603
<b>Age, mean (SD)</b>	(SD)	42.7 (12.1)	36.7 (11.5)	0.96 (0.92-0.99)	0.015	0.96 (0.92-1.00)	0.080
<b>BMI, mean (SD)</b>	(SD)	41.0 (6.5)	42.9 (6.4)	1.05 (0.98-1.12)	0.148	1.07 (0.99-1.17)	0.078
<b>Chronic pain n(%)</b>	No	51 (87.9)	41 (91.1)	Ref.	-	Ref.	-
	Yes	7 (12.1)	4 (8.9)	0.71 (0.18-2.52)	0.606	1.00 (0.19-4.96)	0.996

IPILA Intraperitoneal instillation of local anaesthetic

VAS: visual analogue scale

aOR: adjusted odds ratio

CI: confidence interval

SD: standard deviation

BMI: body mass index

LSG: laparoscopic sleeve gastrectomy

OAGB: one anastomosis gastric bypass

RYGB: Roux-en-Y gastric bypass

SADI: Single anastomosis duodenal ileal bypass

Ref: reference category



### *Primary endpoint analysis*

There was a significant difference in pain scores between the two groups in PACU with the IPILA group having lower pain scores both at rest (median VAS 5.0 [2.25-6.0] IPILA vs median VAS 6.0 [5.0-8.0] placebo,  $p=0.04$  ) and on movement (median VAS 5.0 [IQR 3.0-7.0] IPILA vs. median VAS 7.0 [IQR 5.0-8.0],  $p=0.019$ ). Patients receiving IPILA had less severe pain episodes compared to placebo at rest (VAS  $\geq 7$  22% in IPILA group vs. 48.1% in placebo,  $p=0.005$ ) and on movement (VAS  $\geq 7$  28% in IPILA group vs. 59% in placebo,  $p=0.002$ , Table 1). Uni- and multivariable linear and logistic regression analyses were performed to control for potential confounding. Whilst no significant independent effect of IPILA was found on overall mean VAS scores at resting or on movement (Supplementary Table 2 & 3), an independent effect on reduction of high pain scores (VAS  $\geq 7$ ) could be documented at both rest and on movement (adjusted odds ratio [aOR] 0.28, 95%CI 0.11-0.69,  $p=0.007$  and aOR 0.25, 95%CI 0.09-0.62,  $p=0.004$ , respectively, Table 3 & 4).

### *Secondary endpoint analysis*

No significant difference was seen between the IPILA and placebo groups at other post-operative timepoints, in post-operative analgesia intake, antiemetics use nor mean LOS. The mean frequency of requests for opioid analgesia was 1.8 (95% CI 1.5-2.1) per hospitalisation in the placebo group and 1.9 (95% CI 1.56-2.29) in the IPILA group. Mean use of antiemetics was 1.5 times per admission in the placebo group (95% CI 0.1-0.7) and 1.9 times (95% CI 0.2-0.6) in the IPILA group ( $p=0.270$ ). The median LOS was 1.0 days in both placebo (IQR 1.0-2.0) and IPILA groups (IQR 1.0-2.0,  $p=0.63$ ). In addition, there were no significant differences between the groups with respect to the safety endpoints. There were no unexpected reoperations, no unplanned ICU admission and no mortality. The only complication was a pulmonary embolus (PE) in one patient in the IPILA arm. There were five unplanned readmissions in the IPILA group and four in the placebo group, all for patients who required IV rehydration.

### Chapter 3: Extended discussion

In this study, patients who received IPILA had significantly lower pain scores in PACU. Equally, IPILA was independently associated with a reduction in the likelihood of patients experiencing extreme pain scores. Although not significant, pain scores were also lower at all other time points in the IPILA group up to four hours post-surgery. This is consistent with the half-life of ropivacaine being 4.2 hours [19] by which stage the patients have progressed from recovery to ward-based care. It is also important to consider possible confounders and their potential impact on post-operative outcomes. Uni- and multivariable linear and logistic regression analyses were conducted in order to control for multiple variables including surgery type, hiatus hernia repair, age, BMI and chronic pain when determining the effect of the IPILA intervention. These analyses showed IPILA was the only variable which had significantly lower adjusted odds ratios of severe pain episodes in PACU at rest and on movement. We hypothesised that a reduction in pain immediately post-operatively allows for reduced administration of opioids and hence nausea, facilitating quicker recovery and shorter LOS. However, this was not evident in the results with total opioid use, antiemetic use and LOS being equivalent between the two groups. This is perhaps explained by an already short mean LOS of only 1 day.

Studies have been conducted on several bariatric procedures such as SG, RYGB, SADI and gastric banding using varied methods of intraperitoneal local anaesthetic [12, 22-25, 29]. Most studies demonstrate a significant improvement in pain immediately post-operatively when utilising the intraperitoneal instillation method with which the current study's results are consistent. In a study using intraperitoneal ropivacaine by Ruiz-Tovar [23] reduced post-operative pain scores, lower morphine consumption, earlier time to mobilisation and shorter hospital stay were observed in patients undergoing SG and RYGB. Intraperitoneal instillation has also been combined with surgical site injection of bupivacaine with significantly prolonged time to first post-operative analgesia request in the treatment group [22]. El Sayed & Abdelsamad [23] found that patients in the control group asked for analgesia more than three times sooner ( $102.5 \pm 10.3$  mins) than the group that had received a combination of injected and intraperitoneal bupivacaine ( $328.8 \pm 32.4$  mins). The use of longer acting bupivacaine with the combined injected and intraperitoneal

technique may have contributed to more localised and prolonged analgesic effects that vary from the methods used in our study. Analgesic effects of intraperitoneal bupivacaine have even been extended to 2hrs post-operatively when an increased dose is used, and the patient is kept in the Trendelenburg position for 5 minutes post instillation [24]. A study by Schipper *et al.* [29] is one of very few which has found no significant analgesic effects of 20mL intraperitoneal bupivacaine (2.5%) when observing pain score and opioid use. Although the pain scores were generally lower in the treatment group, no significant difference was observed. There was also no difference between groups in opioid antiemetic use or length of stay. Other studies using bupivacaine have used a greater volume of 40ml 2.5% [22] which may contribute to the reduced analgesic effects observed.

Although the analgesic effects of intraperitoneal local anaesthetic are observed in the majority of studies, methodology was variable. There are variances in the primary outcomes and methods used to assess these, as well as the type of local anaesthetic used. Most studies have used bupivacaine [12, 22, 24-28, 29] with very few using ropivacaine as an option [23]. Ropivacaine was the local anaesthetic of choice in this study due to its decreased cardiotoxicity and central nervous system toxicity when compared with bupivacaine [19]. Similar to Ruiz-Tovar *et al.* [23] who also used ropivacaine as their local anaesthetic, the current study demonstrated significantly reduced post-operative pain scores.

### *Strengths and weaknesses*

This study utilised a robust methodology, namely a double-blinded prospective randomised control trial. We chose to include a range of primary and revision procedures in our study, which increases the generalisability of our results. It can be considered that the small number of non LSG procedures in the sample may dilute the treatment effect, however a subgroup analysis of only LSG procedures was conducted yielding the same results. In order to avoid repetition of this data, the subgroup analysis was not included in the manuscript. In addition, all procedures were carried out by the same surgeon and anaesthetist minimising variation in procedural technique, anaesthetic protocol and ASA grading which can vary based on the anaesthetist assessing the patient. A standardised approach was maintained

when administering the local anaesthetic solution by calculating dosage at 0.5ml/kg according to weight on the day of surgery. This ensured patients were receiving safe and proportionate amounts of analgesia which is particularly important when considering substantial weight variations in patients with obesity. Our study uses a simple method of instillation utilising a simple spraying cannula attached to a 20ml syringe. This is readily available, adds little time to the operation and avoids using expensive and complex devices to aerosolise or nebulise local anaesthetic.

Although this study provides important data on intraperitoneal local anaesthetics in bariatric surgery, the results need to be considered in the context of each surgical team. Variations in anaesthetic protocol can significantly affect outcomes for patients depending on amounts of intraoperative analgesia and antiemetic given. Surgical technique variability and operator preferences such as port site infiltration of local anaesthetic and pneumoperitoneum settings can impact the amount of pain experienced post-operatively. Insufflation rate is an important consideration as Ozdemir *et al.* [30] argue that a lower flow rate and pressure can reduce pain scores post-operatively. The current study used a flow rate of 10L/min with a pressure of 14mmHg which is towards the higher end of recommended pressures [30], however low insufflation pressure and rate decrease the view for the surgeon thus potentially prolonging the procedure.

Pre-operative analgesia requirements due to chronic pain is an important consideration. In this study, similar proportions of patients with chronic pain were included in each group, minimising bias towards a particular group. Patients in this study were given amounts of local anaesthetic tailored to weight, however, no alterations were made on preoperative opioid tolerance. Thus, there may have been potentially less effect of the intervention in patients with a higher opioid tolerance. Furthermore total opioid or antiemetic use was not calculated due to limited data collection and therefore morphine equivalents could not be calculated which would have certainly added to the validity of this variable. Recording other variables such as mean oxygen saturation, desaturation and apnoeic episodes would have provided useful information however were not considered in the design of this trial. We included revision procedures in our study cohort as their inclusion reflects an expected case-mix of surgeries done by a bariatric surgeon. However, it is also

important to consider that patients undergoing revision surgery may often have longer and more complex surgeries, potentially with slower recovery and increased pain.

Although the primary outcome measure of this study was reduction in post-operative pain, there was also a secondary focus on reduction in LOS. Given the study is focusing on the outcome of post-operative pain, it could be assumed the study is underpowered to determine if there is any impact on LOS. Furthermore with the application of ERAS principles, we have refined pre and post-operative care to a point close to maximal efficiency and optimised recovery. Thus altering only one aspect of care may not yield a clinically significant outcome such as reduced LOS. Although the study has had a positive result for the primary outcome, it is only during a very short period of time. Hence this intervention has been abandoned in our practice as it does not yield a benefit which justifies the time and resources utilised for the intervention. However with some optimisation and improvements in this technique, it can be put into regular use in the future. Adjustment of local anaesthetic dosing, using manoeuvres such as reverse Trendelenburg after infiltration and adjusting pneumoperitoneum insufflation pressures may all be possible alterations to this technique to optimise its outcomes. It would also be beneficial to evaluate quality of life data in a future study once the technique has been refined.

## **Conclusion**

This study hypothesised the application of local anaesthetic would eliminate gas pain and allow for reduced LOS. Upon evaluation of intraperitoneal local anaesthetic, we determined that it was only effective in reducing post-operative pain in the recovery room. Utilising a different approach where we focused on weight-based dosing of local anaesthetic did not appear to have any improvement in outcomes when compared to other studies, however, it was a safe technique and there were no adverse outcomes as a result of the local anaesthetic. As a result of our findings, once the data was analysed we have abandoned the use of this practice. However, there is certainly further scope for refinement of this technique. For example, placing the patient in the Trendelenburg position for 5 minutes post instillation or considering higher doses of local anaesthetic could result in prolonged analgesia. Although these results are not clinically significant, this paper makes a significant contribution to literature, and opens the discussion for further enhancement of this technique.

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## Appendix

Supplementary Table 1. Anaesthetic baseline data

	<b>Total (N=104)</b>	<b>IPILA (N=50)</b>	<b>Placebo (N=54)</b>	<b>p-value</b>
<b>TIVA</b>				0.695
Yes	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Inhaled vapour anaesthetic</b>				0.695
Yes	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Muscle relaxant</b>				0.334
No	1 (1.0%)	0 (0.0%)	1 (1.9%)	
Yes	103 (99.0%)	50 (100.0%)	53 (98.1%)	
<b>Opioid anaesthetic</b>				0.821
No	78 (75.0%)	38 (76.0%)	40 (74.1%)	
Yes	26 (25.0%)	12 (24.0%)	14 (25.9%)	
<b>Opioid quantification</b>				0.154
fentanyl (non-documented dose)	1 (4.0%)	1 (9.1%)	0 (0.0%)	
fentanyl 150mg	21 (84.0%)	10 (90.9%)	11 (78.6%)	
fentanyl 175mg	3 (12.0%)	0 (0.0%)	3 (21.4%)	
<b>Regional block</b>				0.695
No	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Nitrous oxide use</b>				0.695
No	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Adjuncts (non-specified)</b>				0.695
Yes	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Tramadol use</b>				0.695
Yes	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Parecoxib</b>				0.695
Yes	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Ketamine</b>				0.695
Yes	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Caldolor</b>				0.695
No	104 (100.0%)	50 (100.0%)	54 (100.0%)	
<b>Antiemetic use</b>				0.937
No	4 (3.8%)	2 (4.0%)	2 (3.7%)	
Yes	100 (96.2%)	48 (96.0%)	52 (96.3%)	

IPILA: Intraperitoneal instillation of local anaesthetic

TIVA: Total intravenous anaesthesia

Supplementary Table 2. Uni- and multivariable analysis of factors influencing mean changes in VAS scores at rest

		<b>Univariable coefficient (95%CI)</b>	<b>p-value</b>	<b>Multivariable coefficient (95%CI)</b>	<b>p-value</b>
<b>IPILA</b>	No		-		-
	Yes	-1.01 (-2.14–0.13)	0.082	-0.88 (-2.07–0.32)	0.148
<b>Surgery type</b>	LSG		-		-
	OAGB	1.56 (-0.20–3.32)	0.082	1.91 (0.14–3.68)	0.035
	RYGB	0.19 (-1.52–1.89)	0.829	0.75 (-1.05–2.54)	0.41
	SADI	0.83 (-2.17–3.83)	0.585	1.04 (-1.98–4.06)	0.494
<b>Concomitant hiatus hernia repair</b>	No		-		-
	Yes	-1.35 (-2.64–0.06)	0.041	-1.07 (-2.49–0.36)	0.14
<b>Age</b>		-0.03 (-0.08–0.01)	0.162	-0.02 (-0.08–0.03)	0.383
<b>BMI</b>		0.05 (-0.03–0.14)	0.228	0.06 (-0.03–0.16)	0.209
<b>Preoperative chronic pain</b>	No		-		-
	Yes	-0.22 (-2.09–1.65)	0.817	0.32 (-1.72–2.36)	0.756

IPILA: Intraperitoneal instillation of local anaesthetic

VAS: visual analogue scale

aOR: adjusted odds ratio

CI: confidence interval

BMI: body mass index

LSG: laparoscopic sleeve gastrectomy

OAGB: one anastomosis gastric bypass

RYGB: Roux-en- Y gastric bypass

SADI: Single anastomosis duodenal ileal bypass

Supplementary Table 3. Uni- and multivariable analysis of factors influencing mean changes in VAS scores on movement

		<b>Univariable coefficient (95%CI)</b>	<b>p-value</b>	<b>Multivariable coefficient (95%CI)</b>	<b>p-value</b>
<b>IPILA</b>	No		-		-
	Yes	-1.21 (-2.44 to 0.03)	0.055	-1.05 (-2.34 to 0.24)	0.109
<b>Surgery type</b>	LSG		-		-
	OAGB	1.57 (-0.34 to 3.48)	0.107	2.03 (0.12 to 3.94)	0.038
	RYGB	0.46 (-1.40 to 2.31)	0.626	1.11 (-0.83 to 3.05)	0.259
	SADI	1.28 (-1.98 to 4.54)	0.438	1.35 (-1.91 to 4.61)	0.414
<b>Concomitant hiatus hernia repair</b>	No		-		-
	Yes	-1.07 (-2.49 to 0.35)	0.139	-0.63 (-2.16 to 0.91)	0.421
<b>Age (range)</b>	18- 67	-0.05 (-0.10 to 0.00)	0.062	-0.04 (-0.10 to 0.01)	0.143
<b>BMI (range)</b>	29-61	0.06 (-0.04 to 0.16)	0.214	0.07 (-0.03 to 0.17)	0.19
<b>Preoperative chronic pain</b>	No		-		-
	Yes	-0.42 (-2.45 to 1.61)	0.685	0.30 (-1.90 to 2.50)	0.787

IPILA: Intraperitoneal instillation of local anaesthetic

VAS: visual analogue scale

aOR: adjusted odds ratio

CI: confidence interval

BMI: body mass index

LSG: laparoscopic sleeve gastrectomy

OAGB: one anastomosis gastric bypass

RYGB: Roux-en- Y gastric bypass

SADI: Single anastomosis duodenal ileal bypass