THE EFFECT OF INTRAPERITONEAL LOCAL ANAESTHETIC INSTILLATION AND INFUSION ON FUNCTIONAL RECOVERY FOLLOWING COLECTOMY

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Abstract

Purpose Intraperitoneal local anaesthetic (IPLA) is a new analgesic technique for inclusion in the polypharmacy approach to postoperative pain management in enhanced-recovery-after-surgery (ERAS) programs. This study determines the effect of IPLA on postoperative pain and functional recovery in patients undergoing colectomy.

Methodology Multi-site, double-blinded, randomized, placebo-controlled trial design: ClinicalTrials.gov Identifier NCT02449720. Adults undergoing colectomy (35 open; 51 laparoscopic) received i.p. ropivacaine 100mg instillation both pre- and post-dissection and 20mg/hr continuous postoperative infusion for 48hrs (IPLA group), or a normal saline equivalent (Control Group). A standardised ERAS program was used in perioperative care. Data collected included baseline demographics, functional postoperative recovery using the surgical-recovery-scale (SRS), postoperative pain using a visual-analogue-scale (VAS), opioid consumption, use of rescue ketamine, recovery of bowel function, time-to-readiness-for-discharge (TRD), and perioperative complications. Participants were followed for 45 days.

Results Eighty-six participants were recruited (IPLA n=44; Control n=42). The IPLA group reported improved SRS scores at day 1 and 7, lower pain scores, required less rescue ketamine, and passed flatus earlier than the Control group ($P<0.05$). The improved SRS at day 7 and pain scores remained present when the subset of participants undergoing laparoscopically-assisted colectomy were considered separately. There was no difference between the groups in opioid consumption or TRD.

Conclusion Instillation and infusion of intraperitoneal ropivacaine for patients undergoing colectomy is safe, decreases pain, and improves functional recovery. We recommend routine inclusion of IPLA into the multimodal analgesia component of ERAS programs for colectomy.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Signed:…… …..……

Date:……2nd Feb 2018…….

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List of Abbreviations

A	ACTH	adrenocorticotrophin releasing hormone
	ADL	activities of daily living
	AF	atrial fibrillation
	ANOVA	analysis of variance
	APR	Abdominoperineal Resection
	ASA	American Society of Anesthesiologists
	AUD	Australian dollar
B	BD	bis in die (twice daily)
	BMI	body mass index
	BP	blood pressure
C	CES-D	Centre for Epidemiological Studies-Depression Scale
	CI	confidence interval
	Cmax	The maximum (or peak) serum concentration that a drug achieves in a specified compartment of the body after the drug has been administrated and prior to the administration. of a second dose
	CO	cardiac output
	CONSORT	Consolidated Standards of Reporting Trials
	CNS	central nervous system
	CPR	cardiopulmonary resuscitation
	CrCl	creatinine clearance
	CRF	chronic renal failure
	Cr-POSSUM	Physiologic and operative severity score for the enumeration of mortality and morbidity (for colorectal surgery patients)
	CV	coefficient of variation
	CYP	cytochrome P450
D	d	days

E	ECG	echocardiogram
	EF	ejection fraction
	ERAS	enhanced recovery after surgery
FG	g	grams
	g-mean	geometric mean
	GFR	glomerular filtration rate
H	h	hours
	HREC	human research ethics committee
I	ICFS	identity consequence fatigue scale
	IDC	indwelling catheter
	IM	intramuscular
	IP	intraperitoneal
	IV	intravenous
	IPLA	intraperitoneal local anaesthesia
	IRR	incidence rate ratio
	IQR	interquartile range
JKL	l	litre
	LOS	length of stay
M	µg	microgram
	MED	milli-equivalent doses
	min	minutes
	mg	milligram
	ml	millilitre
N	NHMRC	National Health and Medical Research Council
	NIH	neuro-immuno-humoral
	NGT	nasogastric tube
	NRS	numeric rating scale

	NSAID	non-steroidal anti-inflammatory drug
OP	PARU	post-anaesthesia recovery unit
	PCA	patient controlled analgesia
	pH	acidity
	PQRS	postoperative quality of recovery
	PPV	positive predictive value
	PRN	pro re nata (as the circumstances arise)
Q	QoR	quality of recovery
R	RR	respiratory rate
	RCT	randomised controlled trial
	RSB	rectus sheath block
	RTSC	ropivacaine toxicity screening chart
S	SAE	severe adverse event
	SaO_2	oxygen saturation
	SC	subcutaneous
	SD	standard deviation
	SEM	standard error of the mean
	SPSS	Statistical Package for the Social Sciences
	SRS	surgical recovery scale
	SSRI	selective serotonin reuptake inhibitor
	STAI	State-Trait Anxiety Inventory
T	TAP	transversus abdominis plane
	TEDS	thromboembolic deterrant stockings
	TGA	Therapeutic Goods Administration
	TRD	time ready for discharge
	TAP	transversus-abdominis plane
	Tmax	The time at which the C_{max} is observed.

UV	ULAR	Ultra-low Anterior Resection
	VAS	visual analogue scale
	VTE	venous thromboembolism
W	WHO	World Health Organisation

XYZ

1. Literature Review

Intraperitoneal local anaesthetic (IPLA) is a promising new analgesic technique that could be used as part of the polypharmacy approach to manage postoperative pain in patients undergoing abdominal surgery. Following open colectomy, augmentation of epidural analgesia with an intraoperative instillation and postoperative infusion of IPLA was shown to not only reduce pain, but also to improve functional recovery, decrease the time to flatus, and reduce circulating cytokines and cortisol[1]. Not all patients requiring colectomy are managed with epidural anaesthesia, there is therefore a need to expand upon the findings of the prior study by assessing the effect of intraoperative instillation and postoperative infusion of IPLA on functional recovery in patients undergoing colectomy under general anaesthesia.

1.1 The Current Standard of Perioperative Care for Patients Undergoing Colectomy

Currently, the evidence-base for optimal management of patients undergoing colectomy recommends surgery, where possible, by the minimally invasive laparoscopic approach in the setting of an optimised enhanced-recovery-after-surgery (ERAS) program[2].

1.1.1 Minimally Invasive Surgery for Colectomy

Open and laparoscopically-assisted colectomy are internationally accepted as having equivalence in surgical and oncological outcome[3]. The laparoscopic approach, however has the additional benefits of reduced postoperative pain and analgesia use, shorter length of ileus, lower morbidity, faster recovery and a shorter hospital stay when compared with the open approach[4-8]. The benefits of the laparoscopic approach can be augmented by addition of perioperative management that involves an established enhanced-recovery-after-surgery (ERAS), or fast-track program [9].

1.1.2 ENHANCED RECOVERY AFTER SURGERY (ERAS)

The concept of an ERAS program was introduced by Kehlett in 1999[10]. These programs prescribe a list of interventions with independent evidence for improvement of a component of postoperative recovery or reduction of morbidity, and when integrated as a patient care program have been demonstrated to reduce complication rates and length of hospital stay in both young and elderly patients[11] without increasing readmission rates[12 13] and to be both clinically efficacious and cost effective across a variety of surgical specialties[14]. Some of these interventions include preoperative patient education and preoperative assessment, which allows for reduction in the emotional contribution to postoperative surgical stress, optimisation of pre-exisiting organ dysfunction, and improvement of physiological reserves; pre-operative glucose loading and early introduction of enteral nutrition, which has been shown to reduce postoperative insulin resistance[15]; minimisation of tubes, drains, and catheters to reduce immobility and infection rates; and temperature control shown to have implications for coagulopathy[16 17].

ERAS interventions that aim to achieve a reduction in the incidence or duration of postoperative ileus are particularly relevant to patients requiring colectomy. Postoperative ileus is a transient impairment of bowel motility following surgery and is clinically diagnosed by the presence of abdominal distension and decreased or absent bowel sounds, lack of passage of flatus or stool and inability to tolerate oral diet. The rate of ileus following abdominal surgery has been determined at 10.3%[18], with ileus following colectomy more likely at rates of 15-25%[19]. Ileus resulted in a nearly doubled length of stay (LOS), total cost of admission and 30 day all-cause readmission rate[18 19]. The interventions that influence the presence and duration of ileus following colectomy include avoidance of hypervolemia, as it is well established that fluid excess increases morbidity and LOS for patients that have

undergone abdominal surgery [20] [21], early introduction of enteral nutrition, and the polypharmacy approach to pain relief.

A further important component of an optimised ERAS program is the provision of adequate analgesia[22]. Good analgesia allows unencumbered respiration and early mobilisation, both independent factors for prevention of a common perioperative complication, pneumonia. Depending on the modality, analgesia also variably contributes to a reduction in the pain-induced stress response to surgery. The surgical stress response is an umbrella term historically used to encompass the endocrine, metabolic and inflammatory responses to injury that are incurred by surgery. These responses include an increase in adrenocorticotropin (ACTH) and circulating cortisol, and an associated relative insulin resistance[23] [24], increase in circulating sympathomimetic agents and inflammatory mediators, in particular the interleukins. As the understanding of this physiological response to injury and inflammation has developed the 'surgical stress response' has more accurately been described as the neuro-immuno-humoral axis.

An optimised ERAS program promotes a polypharmacy approach to adequate postoperative analgesia in order to minimise the use of opioids. Opioids are well known to provide analgesia through varying affinity with their mu, delta and kappa receptors, but also have a well-established side effect profile including sedation, euphoria, respiratory depression, nausea, constipation and physical dependence. Opioids are known to stimulate delta receptors on the bowel resulting in decreased motility, thereby contributing to the pathogenesis of ileus [25] [26]. Thus, minimisation of opioids improves post-operative nausea and vomiting and reduces the incidence and duration of ileus.

Analgesic agents used within a polypharmacy approach to postoperative analgesia for patients undergoing colectomy currently include the opioids, but also combinations of paracetamol

(acetaminophen), cox-2 selective non-steroidal anti-inflammatory drug (NSAID), and regional anaesthetic techniques such as wound infiltration and transversus-abdominis plane (TAP) block, intravenous lidocaine infusion, and spinal or epidural local anaethestic[27].

1.1.3 THE USE OF LOCAL ANAESTHETIC AGENTS FOR POSTOPERATIVE ANALGESIA

To date, thoracic epidural analgesia has the best developed evidence base of all the local analgesic techniques for colectomy and was traditionally considered the gold standard analgesic technique for use in open colectomy. For both open and laparoscopic colectomy there is level 1 evidence that thoracic epidural analgesia provides improved postoperative pain scores [28 29] and results in improved recovery of bowel function[30], and a decrease in duration of ileus[31] when compared with patient controlled parenteral opioid. Then again, epidural analgesia also has a risk of adverse effects, including incomplete block, and level 1 evidence for an increase in incidence of urinary retention (OR 4.3 (1.2 to 15.9)) and a marked increase in incidence of arterial hypotension (OR 13.5 (4.0 to 57.7)[31 32]. In laparoscopic colectomy a series of RCTs have demonstrated that TAP blocks are not inferior to thoracic epidural analgesia in analgesic effect, have a significantly lower incidence of arterial hypotension [33 34], and may result in an improvement in nausea, vomiting, rates of ileus[35] and length of stay[36]. In laparoscopic colectomy, intraoperative intravenous lidocaine infusions result in decreased postoperative pain, reduced fentanyl consumption[37 38], a quicker recovery of gut function and shorter length of stay[38 39] during the first 24 hours following surgery when compared with control normal saline. Non-inferiority of intravenous lidocaine compared with epidural analgesia has been described, however only in a single RCT with study arms of approximately 20 participants undergoing open colectomy[40].

A lesser known analgesic technique that could be used as part of the polypharmacy approach to reduce pain during the post-operative recovery phase is intraoperative instillation of intraperitoneal local anaesthetic (IPLA). There is level 1 evidence that IPLA as an intraoperative bolus dose reduces postoperative pain following laparoscopic gynaecological procedures[41], laparoscopic gastric procedures[42], laparoscopic cholecystectomy[43], and level 2 evidence for pain reduction following open hysterectomy[44 45], laparoscopic appendicectomy[46] and laparoscopic colectomy[47], when compared with parenteral opioids alone.

The theorised mechanism of action for the analgesic effect of IPLA is particularly interesting. IPLA acts to modulate the vagally-mediated neuro-immuno-humoral axis response to the visceral peritoneum injury [48-54] that is incurred by surgery. In any individual, injury, infection, or bowel handling stimulates visceral peritoneal mesothelial and local immune cells to release cytokines. These activate nociceptive vagal afferent nerve endings that are present in visceral peritoneum [55 56]. Stimulatory vagal transmission to the nucleus of the tractus solitarius and dorsal motor nucleus of the vagus [50] is integrated with information from other sources and has two prominent effects, altered perception of visceral pain and activation of the cholinergic anti-inflammatory pathway. The role of the cholinergic anti-inflammatory pathway is to modulate the peritoneal inflammatory cascade through vagal efferent neuronal signalling that culminates in nicotinic cholinergic inhibition of intraperitoneal macrophage activation and cytokine production [49 57-60]. It is therefore a a negative feedback loop that acts to reduce the magnitude of the inflammatory response to intraabdominal injury. IPLA is thought to induce decreased perception of visceral pain and dampening of the surgical stress response through activation of the cholinergic anti-inflammatory pathway [49 57-60]. IPLA administration has been shown to reduce circulating levels of cytokines IL-6, IL-8, TNF-α and cortisol [1 43 61 62], and peritoneal cytokine (IL-6, IL-10 and TNF-α) levels during the first 24hrs following colorectal surgery, and levels of these

cytokines have been directly related to the trajectory of postoperative fatigue experience for 2 months[63].

In a key study by Kahokehr and colleagues patients undergoing colectomy within an ERAS protocol were managed with epidural analgesia, and it was then determined if a postoperative infusion of IPLA as an adjunct to an intraoperative bolus dose would have any benefit. This study demonstrated that augmentation of epidural analgesia with IPLA instillation and 48hr postoperative infusion following colectomy, not only reduced postoperative pain and nausea but also improved functional recovery, time to flatus, and interestingly significantly lowered circulating cytokines IL-6, IL-8, TNF-α, and cortisol within the first postoperative week[1], consistent with the proposed mechanism of action of IPLA. In this study, which demonstrated the potential benefits of IPLA above and beyond simple analgesia, 92% of participants underwent colectomy by the open approach. The effect of IPLA as an intraoperative bolus followed by postoperative infusion in patients undergoing laparoscopic colectomy is therefore yet to be determined. In laparoscopic colectomy use of epidural analgesia is not the gold standard, and in the absence of an epidural infusion of local anaesthetic there is capacity to administer a greater dose of local anaesthetic by the intraperitoneal route, with potentially a greater effect on postoperative recovery. This holds true for patients undergoing open colectomy where epidural analgesia is contraindicated.

1.2 Postoperative Recovery: Definition and Assessment Methods

To date there is no published consensus of the definition or assessment method of postoperative recovery. It can be divided into early, intermediate and late phases equivalent to the time from termination of anaesthesia until recovery of protective reflexes, then time from recovery of protective reflexes until readiness for discharge to home and finally the time from discharge until return to

baseline preoperative function and well-being some weeks to months following surgery[64 65]. The concept of post-operative recovery following bowel surgery has shown temporality in its evolution from publication to publication, and has been described as multiple domains, rather than a single entity. To date, the domains of recovery have included fatigue, patient satisfaction, the post-discharge return to normal functioning in both cognition and activities of daily living, pain, return of normal bowel function, time to readiness for discharge (TRD) or length of hospital stay (LOS), and post-operative complications.

A number of postoperative recovery or quality-of-life assessment tools have been developed for use in English-speaking inpatients as a primary outcome measure at a variety of time-points [66-72], and held-up for comparison with the eight standardised validation quality criteria for health status questionnaires[73 74] that were outlined by the Scientific Advisory Committee of the Medical Outcomes Trust [75] and in a follow up paper by Terwee and colleagues [76]. The best validated and most widely used of these Quality of Recovery Tools are the Quality-of-Recovery(QoR)-40 tool[66 77] and its short-form version the QoR-15[71], the Surgical Recovery Scale[68], and the Postoperative Quality of Recovery (PQRS)[67] tool, but none of these assess all the domains of recovery (Table 1) .

As opposed to the QoR-40, -15 and PQRS that were designed by anaesthetists with an interest in post-operative recovery from an anaesthetic perspective, the SRS was designed by a psychologist expert in fatigue in collaboration with a group of general surgeons. The aim of the SRS is to assess fatigue, vigor, mental function, impact on patient activity and impact on ADLs as a percent of maximum score, in post- laparoscopic and open abdominal surgical patients at multiple time-points. It is a 13- item scale adapted from the longer 31-item Identity-Consequence Fatigue Scale (ICFS) published in 2005[70], and validated against 7 of the 8 quality criteria[68]. It is important to note that the discriminant validity of the ICFS has been proven, such that principal components analysis shows all

sub-scales are distinctive from depression and anxiety as determined by the State-Trait Anxiety Inventory (STAI) and Centre for Epidemiological Studies-Depression Scale (CES-D). This tool includes baseline patient data and temporal assessment of recovery domains at baseline, and day 3, 7, 30 and 60 postoperation.

Table 1.1: Comparison of validated Quality of Recovery Tools

Recovery Parameters	**QoR-40**[66 77]	**QoR-15**[71]	**SRS**[68 70]	**PQRS**[67 74]
Pain	Yes	Yes	No	Yes
Normal bowel function	No	No	No	No
Fatigue	Yes	No	Yes	No
Patient Satisfaction	Yes	Yes	No	Yes
Cognition	Concentration	No	Concentration	Yes
Psychosocial function/Emotions	No	Yes	No	Yes
ADLs/Physical Independence	Yes	Yes	Yes	Yes
Composition / Timing of Tool	40 item composite score. At postoperative 24hr	15 item composite score. At postoperative 24hr	13 item composite score. Baseline, day 3, 7, 30 and 60 postoperation	22 item dichotomous score. Baseline, 15 min, 40 min, days 1 and 3 postoperation

There are numerous assessment methods for pain. Due to the complex and subjective nature of pain a valid and reliable objective outcome measure has never been developed. In the literature, the most commonly used method to assess acute abdominal pain or postoperative pain following abdominal surgery is the Visual Analogue Scale (VAS). The VAS is presented as a 100 mm line, with no numbers but verbal descriptors, usually ‘no pain’ and ‘worst imaginable pain’ at the polar ends of the line. The

patient is asked to mark the line at their perceived level of pain intensity. The length from the no pain end to the patient mark in mm is the pain score. A variation of this with similar sensitivity is the Numeric Rating Scale (NRS) where the line is numbered from 1 to 10[78]. There is limited and ongoing work regarding the clinical interpretation of particular pain scores, and what magnitude change score is clinically revelant once a statistical difference in pain scores has been obtained. It has been suggested that in the postoperative setting 0 to 4 mm can be considered no pain; 5 to 44 mm, mild pain; 45 to 74 mm, moderate pain; and 75 to 100 mm, severe pain[79]. When either post-laparotomy pain or acute abdominal pain is managed with opioids, a minimal change in VAS of 10-17mm has been shown to produce a clinically relevant level of analgesia as assessed by self reported change in pain[79-81]. Separately, a change in VAS that is associated with a reduction in opioid consumption may be considered clinically relevant.

Postoperative gut dysfunction involves both the stomach, small bowel and colon, and is multifactorial in etiology. The mechanisms include: impaired myotonic contractions as a result of altered electrolyte and fluid balance; oxidative stress associated with relative intestinal ischaemia; smooth muscle relaxation due to the direct effect of particular inflammatory mediators i.e., nitric oxide [82]; modulation by the NIH-axis [50]; and opioid agonism of the myenteric plexus μ-receptor with subsequent inhibition of acetylcholine release and increased smooth muscle tone [82]. Indicators of recovery of gastrointestinal transit are the combined outcome measures of tolerance of solid food and defecation (PPV 93% for scintigraphic evidence of colonic transit)[83], or the passage of flatus[84].

The time to readiness for discharge (TRD) is a validated measurement of short-term recovery after colorectal surgery[85]. Discharge criteria were defined as passage of flatus or bowel motion, tolerance of oral diet and absence of nausea and vomiting, mobilisation back to baseline function, analgesia requirement managed with oral tablets only, and willingness to be discharged home.

1.3 The Efficacy and Safety of Intraperitoneal Ropivacaine for Postoperative Analgesia

As described previously, the effect of IPLA as an intraoperative bolus followed by postoperative infusion in patients undergoing laparoscopic colectomy is yet to be determined, and in the absence of an epidural infusion of local anaesthetic there is capacity to administer a greater dose of local anaesthetic by the intraperitoneal route, with potentially a greater effect on postoperative recovery, while still avoiding development of clinical and serum toxicity. Ropivacaine is currently known as the safest long acting local anaesthetic due to a better cardiac toxicity profile [86] and higher plasma concentration achieved prior to toxicity when compared with alternatives such as bupivacaine [41 87]. It is therefore appropriate to review the current literature that assesses the analgesic efficacy, and clinical or serum toxicity of intraperitoneal ropivacaine, to determine what dose would be most effective and safe in this setting.

There are currently eighteen blinded randomised controlled trials that compare intraperitoneal ropivacaine with placebo normal saline to determine analgesic effect and assess for clinical signs or symptoms of local anaesthetic toxicity. Ropivacaine was administered into the peritoneal cavity during abdominal surgery by nebulisation in five (Table 1.2), by instillation in twelve (Table 1.3), and by instillation and postoperative infusion in the study of Kahokehr and colleagues[1] (Table 1.3). There were also seven studies that evaluated both the analgesic effect of ropivacaine and post-administration serum concentrations using gas or liquid chromatography following administration by instillation into the peritoneal cavity during abdominal surgery (Table 1.4). In these studies of ropivacaine pharmacokinetics, the intraperitoneal ropivacaine doses that were used varied between 100 to 300 mg, the mean Cmax ranged from 0.66 to 3.76 microg/ml and mean Tmax ranged from 15 to 35 minutes without adrenaline.

Table 1.2: The analgesic efficacy and clinical toxicity of intraperitoneal ropivacaine by nebulisation.

Reference	Administration route	Ropivacaine doses in mg (concentration)	Operation	Analgesic effect	Clinical signs of toxicity
Kaufman 2008[88]	IP nebulisation	100mg (10ml 1% over 30min)	Laparoscopic gynaecological procedures	Absent	None
Kaufman 2013[89]	IP nebulisation	100mg (10ml 1% over 30min)	Laparoscopic gynaecological procedures	Absent	None
Ingelmo 2013[90]	IP nebulization pre-dissection or post-dissection	30 mg (3ml 1% over 6min)	Laparoscopic cholecystectomy	Present No difference pre- or post-dissection	None
Somaini 2014[91]	IP nebulization pre-dissection, or post-dissection	30 mg (3ml 1% over 6 min)	Laparoscopic gynaecological procedures	Present	None
McDermott 2015[92]	IP nebulization at peritoneal insufflation + pre-incisional trocar site infiltration	75mg (10ml 0.75%) to trocar sites + 50mg (5ml 1%) nebulized	Laparoscopic cholecystectomy + Nissen fundoplication	Absent, present in subgroup analysis by operation type	None

IP - intraperitoneal

The evidence that ropivacaine administered via nebulisation is an effective post-operative analgesic is inconclusive (Table 1.2). An analgesic effect of nebulized intraperitoneal ropivacaine was identified in only two of the five RCTs. These studies were of patients undergoing laparoscopic cholecystectomy and laparoscopic gynaecological procedures, used lower doses of ropivacaine (30-50mg administered over 6min pre-dissection) and assessed analgesia using a 1-100mm Visual Analogue Scale for pain performed within the first 24hr after surgery. No analgesic effect was seen in three of the five studies identified. Two of these were by the same authors and were of patients undergoing laparoscopic gynaecological procedures (unilateral/bilateral salpingo-oophorectomy or unilateral/bilateral ovarian cystectomy), using 100mg ropivacaine administered over 30min, and assessed pain using a labelled 1-10cm Numerical Rating Scale.

Table 1.3: The analgesic efficacy and clinical toxicity of intraperitoneal ropivacaine by instillation

Reference	Administration route	Ropivacaine doses in mg (concentration)	Operation	Analgesic effect	Clinical signs of toxicity
Kang 2010[46]	IP instillation	2mg/kg 100ml	Laparoscopic appendicectomy	Present	None
Dreher 2000[93]	IP instillation	200mg (20ml 1%)	Laparoscopic tubal ligation	Present	None
Kucuk 2007[94]	IP instillation	150 mg (20 ml 0.5%) with 1ml 1:200000 adrenaline	Laparoscopic cholecystectomy	Present	None
Park 2011[47]	(A) IP instillation pre-dissection, or (B) pre- and post- dissection	1 mg/kg each instillation	Laparoscopic colectomy	(A) Present (B) Present and greater than A	None
Karaman 2012[95]	IP instillation	3mg/kg 0.75% diluted to 200ml saline	Laparoscopic gynaecological procedures	Present	None
Somaini 2014[91]	IP instillation	100mg (20ml 0.5%)	Laparoscopic gynaecological procedures	Present	None
Callesen 1999[96]	IP instillation / Trocar site infiltration	285 mg total: 150 mg (30 ml 0.2% to pelvic peritoneum + 12ml 7.5% to mesosalpinx / 135mg (18ml 7.5%)	Laparoscopic sterilisation	Present	None
Pappas-Gogos 2008[97]	IP instillation / Trocar site infiltration pre-dissection	155mg total: 80mg (40ml 0.2%) / 75mg (10 ml 0.75%)	Laparoscopic cholecystectomy	Present	None
Yan 2008[62]	IP instillation + trocar site infiltration	150 mg total: 50mg (10ml 0.5%) / 100mg (20ml 0.5%)	Laparoscopic gastrointestinal surgery (stomach + bowel)	Present	None
Cha 2012[98]	IP instillation / Trocar site infiltration	240mg total: 200 mg (100 ml 0.2%) / 40 mg (20 ml 0.2%)	Laparoscopic cholecystectomy	Present	None
Liu 2015[99]	(A) IP instillation post-dissection, or (B) IP instillation + trocar site infiltration	75mg (10 ml 0.75%) instillation +/- 75mg (10ml 0.75%) infiltration	Laparoscopic cholecystectomy	(A) Reduced opioid consumption, but no change in VAS (B) Present	None
Kahokehr 2011[1]	IP instillation & postoperative infusion + epidural infusion	75mg instillation + 4ml/hr 0.2% solution for 72hr	Open colectomy	Present	Serum
Ruiz-Tovar 2016[100]	IP instillation + trocar site infiltration	300mg ropivacaine (200ml 1.5%)	Laparoscopic sleeve gastrectomy or Roux-en-Y gastric bypass	Present	

IP - intraperitoneal

Table 1.4: The pharmacokinetics of ropivacaine following intraperitoneal bolus administration

Reference	Procedure, N	Timing of administration	Ropivacaine concentration, total mg instilled	Time serum level measured	Serum/clinical toxicity	CMax/TMax (µg/ml)/min	Conclusion
Narchi 1992[101]	Diagnostic laparoscopy, 7	Pre-exploration	120 mg (80 ml 0.125% +1:800000 adrenaline)	0, 1, 3, 5, 10, 15, 20, 30, 40, 60, 90, 120, 180, 240, 360 min		0.92 ± 0.63 (mean ± SD) / 52 ± 24; $t_{1/2}$ 204 ± 47min	Analgesic effect. Serum levels safe
Gupta 2002[102]	Lap chole, 8	Post-dissection	150mg (20 ml 0.5% IP & 10ml 0.5% port sites). Postoperative q4h PCA 50mg prn.	30, 60, 90, 120 min and at 20-24h	None detected	Total 0.9 (median range 0.3-1.8). Median free0.019 / 30	Analgesic effect. Serum levels safe
Bambingoye 2009[103]	Elective ceserean section, 10		225mg (10ml 0.75% IP & 20 ml 0.75% to rectus aponeurosis and subcutaneously	0,15,30,60,120,240,480, 960, 1920 min	None detected	1.6±0.9 (mean ± SD) / 30	Analgesic effect. Serum levels safe. No correlation between body size and serum levels.
Labaille 2002[104]	Lap chole, 19	Pre-pneumoperitoneum (T1) and post-dissection (T2)	G1: 100 mg (20ml 0.25% at T1 & T2). G2: 300 mg (20ml 0.75% at T1 &T2).	0,1,5,10,15,20,40 after T1 and T2	G1: None detected G2: 2 patients had levels >4 µg/ml after T1 and 6 after T2. No clinical toxicity	G1: T1 0.66 / 35 T2 2.34 / 15 G2: T1 2.93 / 30 T2 3.76 / 30	Equi-analgesia between 100mg and 300 mg doses, but serum levels toxicity reached at 300 mg.
Paech 2008[105]	Lap chole and lap gynae procedures		150 mg (20ml 0.75%).	0, 15, 30, 60, 120 min	No clinical or serum toxicity	0.82 / 30	Analgesic effect. Serum levels safe.
McDermott 2014[106]	Lap chole, 5	Trocar site infiltration + IP nebulization at peritoneal insufflation	75mg (10ml 0.75%) to trocar sites + 50mg (5ml 1%) nebulized	0, 10, 20, 30, 60, 90 min	No clinical or serum toxicity	0.98±0.05 / 10-20min; $t_{1/2}$ 108 – 252 min	Analgesic effect not assessed. Serum levels safe.
Yakoshi 2015[107 108]	Lap gynae surgery	Pre-operative RSB then IP instillation	RSB 75mg (20ml 0.375%) + either (A) 50mg (20 ml 0.25%) or (B)100mg (20ml 0.5%) IP	0, 30, 60, 120, 180min post RSB then 0, 5, 12, 30, 45, 60, 90min post IP instillation	No clinical or serum toxicity	Pre IP plasma conc A = 0.52±0.03, B = 0.51±0.02 Cmax A = 0.82±0.04, B = 1.00±0.05 Tmax A = 17.7±2.3, B = 24.4±2.5	Analgesic effect not compared with sham. No difference in effect between A and B.

IP – intraperitoneal; RSB – rectus sheath block

The analgesic effect of ropivacaine instilled into the intraperitoneal cavity as a single bolus dose was consistently demonstrable at a bolus dosing range of 100 -200 mg IP [91 93 94] (Table 1.3). Analgesia was determined as a significant difference in VAS scores at varying time points within the first 24hrs postoperation, by all studies excepting the study of Pappas-Gogos[97], which used a numeric rating scale (NRS). All of the studies reviewed reported differences in VAS that were both significantly different and clinically relelvant[80 81], with seven of twelve studies reporting decreased consumption of opioid [1 46 47 93 94 98 100]. An analgesic effect of a 75mg instillation dose followed by 8mg/hr intraperitoneal infusion of ropivacaine as an adjunct to at 15-20mg/hr epidural infusion of ropivacaine was demonstrated in patients undergoing open colectomy [109] (Table 1.3). It was also shown to was shown to result in an improved functional postoperative recovery as measured by the SRS, and a reduction in systemic cytokine and cortisol concentrations [109]. It is currently unknown whether use of intra-abdominal drain negates the effect of intraperitoneal ropivacaine instillation.

Ropivacaine toxicity is a well documented event. Clinical signs or symptoms of toxicity are produced via the central nervous system, and include perioral numbness, dysarthria, light-headedness, visual and hearing disturbances and muscle twitching, which precede convulsion, coma, respiratory arrest and the cardiotoxic effects of prolonged QRS, and cardiovascular depression [87]. Ropivacaine plasma levels are detectable in great variation following epidural[110] or peritoneal administration[96] and are not correlated to body size[103]. Ropivacaine is predominantly bound to α_1-acid glycoprotein over a range of concentrations, where 2-6% ropivacaine is always in the unbound state [111-113].It is the unbound drug levels that result in serum and clinical toxicity. The maximum tolerated venous plasma concentrations of ropivacaine prior to onset of signs and symptoms of clinical toxicity are reported to be 0.11±0.1 (range 0.01 – 0.38 mg/L) of unbound ropivacaine, and 2.1±1.2 (range 0.8-4.5mg/L) total. At these concentrations ropivacaine increased systolic and diastolic BP and pulse, increased QRS width and decreased EF by 11.6% and CO by 2.5% relative to placebo. No arrhythmia occurred at

this level of toxicity. Once clinical signs of toxicity are established, the time from cessation of infusion to resolution of symptoms is reportedly 13 ±11 min[87].

Ropivacaine toxicity is more likely in patients with hepatic impairment as ropivacaine is metabolised by the liver and excreted by the kidney. Patients with end-stage liver disease have around a 60% lower mean ropivacaine clearance than healthy subjects and are thus expected to have over two-fold higher steady-state ropivacaine plasma concentrations during a continuous ropivacaine infusion[114]. Concurrent use of fluvoxamine, enoxacin, ketoconazole, or cimetidine, potent CYP1A2, 2E1, or 3A4 inhibitors, has been shown to reduce ropivacaine clearance in both *in vivo* and in *in vitro* models. The pharmacokinetics of ropivacaine are not affected by renal failure. While the renal clearance of ropivacaines' main metabolite (S)-2',6'-pipecoloxylidide (PPX) correlates with creatinine clearance, non-renal clearance compensates for reduced renal clearance in most patients[115]. None of the studies reviewed reported the presence of clinical signs or symptoms of ropivacaine toxicity (Table 1.2, Table 1.3, Table 1.4).

Safe serum levels of ropivacaine were demonstrated at an IP bolus dosing range of 100-150mg [104] [105] or pre-dissection bolus of 100mg followed by post-dissection bolus of 100mg approximately 60 minutes apart[104]. At a bolus IP dose of 300mg toxic serum levels begin to be identified in some individuals[104]. With concurrent trocar site infiltration a total dose of 285 mg can be tolerated without clinical evidence of central nervous system or cardiovascular toxicity[96], and 225mg tolerated without development of serum toxicity[103] (Table 1.4). Following ropivacaine infusion by concurrent epidural and intraperitoneal routes to a total dose of 28mg/hr over 72hrs, no clinical toxicity was observed and plasma levels of ropivacaine were below the level at which central nervous toxicity can occur (4.3mg/L[87]) in all excepting two random samples in two separate patients (Table 1.3). This raises the possibility that a ropivacaine infusion of 28mg/hr is at the upper limit of safety.

No other studies employing postoperative infusion of IPLA were identified for review, therefore evaluation of the efficacy and safety of a lower infusion rate is not possible, however, preperitoneal[110 116 117], epidural[113 118 119], transversus abdominis plane (TAP) [120] and peripheral wound infusion[121] rates of 20mg/hr have all separately been shown to be safe. This includes infusions running for up to 48hrs[120], 72hrs[113 119 122 123], 96hrs[123], and 1 month post-operation [121], where the serum levels of unbound ropivacaine remained stable and below the plasma toxicity threshold as the result of a dose and time-dependent increase in the serum levels of binding protein α_1-acid glycoprotein[113 119-121 123-125], total and bound ropivacaine[113 118-125]. The transferability of the safety profile of the 20mg/hr ropivacaine infusions in these studies of alternative routes of administration to the intraperitoneal route depends on the comparability of the absorption profile of ropivacaine by the different routes. While the absorption of ropivacaine from the intraperitoneal compartment has yet to be evaluated in humans, the absorption of ropivacaine in the intraperitoneal compartment of pigs has been shown to replicate the biphasic absorption profile after femoral nerve, spinal, epidural and paravertebral block in humans [126-132]. Separately, the half-life of ropivacaine administered by both the epidural, TAP, RSB, peripheral, rectal and intraperitoneal routes are comparable, at 3-4 hrs [101 131 133 134], implying similar absorption profiles.

1.4 Study Hypothesis and Aims

The aim of this double-blind randomised controlled trial (RCT) is to determine the effect of intraperitoneal local anaesthetic (IPLA) intraoperative instillation and postoperative infusion on postoperative recovery following laparoscopic and open bowel resection in an optimised enhanced-recovery-after-surgery (ERAS) program. We hypothesise that intraperitoneal instillation and infusion of the local anaesthetic ropivicaine to the site of maximal visceral dissection from the time of surgery

to 48 hours post laparoscopic bowel resection in an optimised ERAS setting will result in an improved functional postoperative recovery, as assessed by the SRS. While the SRS is our primary outcome measure for the purpose of determining power for this study, it is important to note that fatigue is not independent of the other domains of postoperative recovery, and that the other domains of recovery have equivalent importance as outcome measures.Therefore, this study also aims to determine the effect of intraperitoneal ropivicaine infusion on postoperative pain, opioid consumption, recovery of bowel function, discharge parameters and postoperative complications.

IPLA has the potential to significantly improve post-operative recovery through the reduction of pain, post-operative nausea and ileus which may have the follow-on effect of a reduction in hospital length of stay and potential reduction in cost to the health system. This research will provide evidence to allow recommendation on the routine inclusion of IPLA into the multi-modal analgesia component of Enhanced Recovery After Surgery programs for laparoscopic colectomy.

2. METHODS

2.1 Participants

The study population included adults undergoing colectomy or reversal of Hartmanns procedure at Royal Adelaide Hospital, St Andrew's Hospital or Calvary North Adelaide Hospital in South Australia. Patients planned for Abdomino-Perineal Resection (APR) or Ultra-Low Anterior resection (ULAR) were not assessed for eligibility as these procedures are associated with use of an intraabdominal drain, and it is not known if use of in intraabdominal drain might negate the effect of intraperitoneal infusion.

Potential participants were invited to participate in the study and provided with an Information Sheet. (Appendix 6.1). Prior to requesting a decision regarding participation the potential participant was encouraged to take the time to read and discuss the information sheet with their next of kin, and to ask the inviting investigator questions. They were reassured that participation was voluntary and there was no disadvantage to them if they decide not to participate.

After obtaining informed consent for participation in the study, eligibility for inclusion was determined based on the following exclusion criteria.

2.1.1 EXCLUSION CRITERIA

Exclusion criteria:

- Under 18 years of age or over age 90.
- Allergy to local anaesthetic.

- Requirement for spinal or epidural anaesthesia rather than general anaesthesia as this is a significant deviation from the proposed anaesthetic protocol.
- ASA ≥ 4 due to the higher likelihood or morbidity and mortality, which may confound resulting data.
- Severe underlying cardiovascular disease including conduction abnormalities, ischaemic heart disease or congestive heart failure, or use of amiodarone as a regular medication due to a higher risk or cardiac arrest under general anaesthetic or during use of local anaesthesia.
- Chronic Renal Failure (CRF) Stage 3 (GFR < 60 based on a single sample within a month prior to operation). The pharmacokinetics of ropivacaine is not affected by renal failure although the renal clearance of its main metabolite (S)-2',6'-pipecoloxylidide (PPX) correlates with creatinine clearance, non-renal clearance compensates for reduced renal clearance in most patients[115].

  GFR will be calculated using the Cockcroft Gault equation for creatinine clearance:

  CrCl ml/min = [140-age(years)] x bodyweight (kg) / R x serumcreatinine (micromol/L)

  R = 0.815 for males, 0.85 for females
- Hepatic dysfunction of Child-Pugh class B or C. Patients with end-stage liver disease have about a 60% lower mean ropivacaine clearance than healthy subjects and are thus expected to have over two-fold higher steady-state ropivacaine plasma concentrations during a continuous ropivacaine infusion[114].
- Concurrent or recent (within 3 months) use of fluvoxamine, enoxacin, ketoconazole, or cimetidine. These are potent CYP1A2, 2E1, or 3A4 inhibitors that have been shown to reduce ropivacaine clearance *in vivo* or in *in vitro* models. Potential participants concurrently using other potent CYP1A2, 2E1, or 3A4 inhibitors, where it is unclear if there

is an effect on ropivacaine clearance, will be included or excluded from the study at the discretion of their study specialist anaesthetist.

- Change in operative plan such that intra-abdominal drain is required, as this may negate the effect of intra-abdominal infusion.
- Intraoperative formation of stoma due to increased ratio of abdominal wall:visceral peritoneum dissection. This exclusion criterion was discontinued in August 2015 to improve recruitment rate.
- Preoperative systemic steroid dependence due to derangement of the inflammatory response.
- Preoperative chronic pain illness including fibromyalgia, chronic regional pain syndrome, chronic fatigue syndrome, non specific chronic pain requiring daily opiate use, and history of alcohol or drug dependence due to the impact these have on subjective interpretation of pain and tolerance to opioid requiring significantly higher dosing regimens.
- Inability to consent or complete data scores in the study questionnaires due to cognitive impairment and/or language barrier.
- Pregnancy or breastfeeding.

2.2 Settings

2.2.1 ROYAL ADELAIDE HOSPITAL (RAH)

The RAH is South Australia's largest public accredited teaching hospital and is the states quarternary referral centre. It has 554 general medical beds, 96 specialty beds, and up to 60 Intensive Care beds. It has a specialist colorectal surgery service. At the RAH 12000 emergency and 10000 elective surgical procedures are performed per year (2011-2012 data).

2.2.2 SAINT ANDREW'S HOSPITAL

Saint Andrews Hospital is a privately run accredited teaching hospital. It is a tertiary hospital of 201 beds located in the central business district of Adelaide. It has 9 operating theatre suites and an 18 bed Critical Care Unit. It has a specialist colorectal surgery service. 12000 theatre procedures are performed per year (2014-2015 data).

2.2.3 CALVARY NORTH ADELAIDE HOSPITAL – CALVARY HEALTH CARE ADELAIDE

Calvary North Adelaide Hospital is a privately run hospital owned by the Sisters of the Little Company of Mary and located in North Adelaide. It is a tertiary hospital of 153 beds (2016 data), 7 theatres specialising in General / Colorectal Surgery, Urology and Gynaecology and an 8-bed Critical Care Unit.

2.3 Drugs and Devices

2.3.1 DRUG: ROPIVACAINE HYDROCHLORIDE 0.2%

The formulation and description of drug Ropicaine Hydrochloride (Kabi Brand), trade name Naropin, is outlined in the Appendix 6.2: NAROPIN Product Information PAIN.000-114-897.7.0 Approved: 13/4/2011.

2.3.2 DRUG: NORMAL SALINE

The formulation and description of drug Sodium Chloride Injection 0.9% is outlined in the Appendix 6.3 : Sodium Chloride Injection 0.9% Product Information. It is approved by the Therapeutic Goods Adminstration of Australia (TGA) for use as a sterile irrigation medium.

2.3.3 DEVICE: ON-Q PAINBUSTER

The On-Q Painbuster (B.Braun Melsungen) is a disposable closed elastomeric pump device for the continuous regulated infusion of local anaesthetic for wound infiltration or regional anaesthesia through a soaker catheter. It is delivered in a single sterile pack of all components: pump, catheter, 60 ml filling syringe, E-clip or carry case, 17G T-peel introducer(s) and sheath(s), 5ml priming syringe, labels. All components are disposable after use. Specifications for this study are Fill volume: 400 ml; Flow rate 10ml.hr; Delivery time 2 days; 25cm soaker catheter. Further product information is outlined in Appendix 6.4: On-Q Painbuster Product Information.

2.4 Study Plan and Design

This study is a prospective double-blind randomised controlled trial (RCT) comparing the effect of intraperitoneal local anaesthetic (IPLA) instillation and infusion on postoperative recovery following laparoscopic and open bowel resection in an optimised enhanced-recovery-after-surgery (ERAS) program, with a normal saline equivalent.The study design is closely aligned with the study design of Kahokehr and collegues[1], and underwent a peer-review process during the design phase. A working group was established, consisting of eight clinical co-investigators, including Colorectal Surgeons, Anaesthetists, a Clinical Pharmacist and senior nursing staff. It was presented for critical evaluation at the Royal Adelaide Hosital Surgery and Gastroenterology Research Meeting and at the Department of Anaesthesia, Hyperbaric and Pain Medicine audit meeting. In addition, members from the working group met together throughout the study to review adherence to protocol, general safety, safety reports, and systems problems to make any necessary recommendations for amendments as required. Of note this working group implemented a number of changes to the study design including discontinuation of the exclusion criterion “Intraoperative formation of stoma” in August 2015 to

improve recruitment rate, the addition of two new recruitment sites (St Andrew's Hospital in August 2015 and Calvary North Adelaide Hospital in November 2015, with both additional sites provided independent Ethics Committee review), and, due to initial overestimation of the recruitment rate and time restrictions, closure of recruitment upon completion of the laparoscopic arm, prior to completion of the open arm.

This RCT was approved by the Investigational Drugs Subcommittee (IDSC) and the Human Research Ethics Committee (HREC) of the Royal Adelaide Hospital on 19 March 2015, and assigned identifiers: HREC/15/RAH/45 Protocol Record 150219. The requirements of the Research Governance Unit were adhered to SSA/15/RAH/164 (MyIP 6436).

This RCT was approved by the HREC of St Andrew's Hospital on 13 July 2015 and allocated Identifier: Project Number 91, and by the HREC of Calvary Health Care Adelaide on 28 October 2015 and allocated Identifier: 15-CHREC-F009.

Registration at ClinicalTrials.gov register was prospective, and resulted in automated registration in the Australian and New Zealand Clinical Trial Register http://www.anzctr.org.au/ and allocation of WHO Universal Trial Number http://apps.who.int/trialsearch/utn.aspx as follows:

Universal Trial Number (UTN) Identifier : U1111-1170-6367

ClinicalTrials.gov Identifier: NCT02449720

This study was conducted in accordance with the ethical principles that have their origin from the declaration of Helsinki and are consistent with ICH/GCP. This study complies with the National Health

& Medical Research Council (NHMRC) National Statement on Ethical Conduct in Research Involving Humans.

2.4.1 RANDOMISATION AND ALLOCATION CONCEALMENT

Randomisation was performed electronically by staff of the Department of Pharmacy, the Royal Adelaide Hospital. Randomisation was stratified by open or laparoscopic colectomy and then performed in a 1:1 ratio in blocks of 4 to Control and IPLA arms with allocation concealment. Where a laparoscopic case was converted to the open approach the allocation would be reissued by pharmacy staff with maintenance of concealment. Staff of the Department of Pharmacy prepared the study experimental solution (medication) prior to the day of surgery and labelled it with a unique identifier that indicated intention for an open or laparoscopic case, but did not indicate which study arm the experimental solution corresponded to. Once a participant received the experimental solution within the study protocol they were allocated the unique identifier of the experimental solution used.

2.4.2 BLINDING

All participants, anaesthetists, surgeons, operating theatre staff and ward-based nursing and medical staff were blinded to the allocated study arm. Emergency unblinding was made available (at the discretion of the investigator) via a request to the on-call pharmacy research technician to disclose the patient study arm. Unblinding events were recorded in the patient's chart and study file and with the reason for unblinding.

2.4.1 POWER CALCULATION

The *a priori* power calculation was carried out using G*Power 3.1 based on the primary outcome of SRS on day 3 (day aimed at for discharge). Based on previously published data a difference of

~10% in SRS at postoperative day 3 between control and intervention arms was considered clinically significant[109]. Using a two-tailed Mann-Whitney test between two independent groups, n=22 per group would be required to detect a difference of 10% between groups at postoperative day 3 with an α-error probability of 0.05 and a power of 0.80. No interim analyses were planned to be carried out.

Based on this calculation and to allow for a withdrawal rate / reoperation rate of 10%, 25 patients were required to be recruited to each arm of both the laparoscopic and open approach cohorts, total = 100.

2.4.2 STANDARD PERIOPERATIVE CARE

Study participants were randomised into two parallel arms - Control and IPLA Group. Both groups received equivalent standardised perioperative care described as follows, with the exception of experimental solution type provided as bolus and 48h infusion.

2.4.2.1 Enhanced recovery after surgery program (ERAS)

Perioperative management of all patients was standardised to minimise variation in patient outcomes by use of an established evidence-based[27] ERAS program (Table 2.1). This program was active at the Royal Adelaide Hospital prior to commencement of this study. At Saint Andrews Hospital the majority of the program was considered standard practice but for the purposes of this study the program in full was implemented, including successful introduction of routine preoperative assessment, patient education and use of pre-operative nutritional drinks. Ward-based staff were provided in-service training regarding adherence to the program. At Calvary North Adelaide Hospital the program was considered standard practice and no changes to practice were implemented.

Table 2.1: Enhanced Recovery After Surgery (ERAS) Program	
Preoperative	
Patient education in preadmission clinic	Detailed counselling regarding perioperative management and expected postoperative progress, reinforcing the expectation of early oral intake, early ambulation and self-care.
	Smoking cessation advice.
	Discharge planning
Bowel Preparation	No routine bowel preparation.
Minimal preoperative fasting	Fast from solids for 6h, from clear fluid from 2h
Preoperative nutritious drink	2 serves the night prior and 2 on day of surgery
Intraoperative	
Intravenous fluids	Aim for euvolemia with crystalloid. Colloid, Albumin, or Red blood cells given only if required.
Antiemetic	IV dexamethasone and ondansetron
Analgesia	1g IV paracetamol, parecoxib, IV tramadol and titrated fentanyl.
Oxygenation	80% oxygen intraoperatively and in recovery
Hypothermia prevention	Minimise exposure, bairhugger, warmed IV fluids
VTE prophylaxis	SC heparin on induction
Vasopressor	Titrated metaraminol or ephedrine for hypotension.
Surgery	Minimally invasive where possible. No routine drains. No routine NGT. Antibiotic prophylaxis (gentamicin + metronidazole).
Postoperative	
Multimodal analgesia regimen	Fentanyl PCA
	Regular paracetamol (1g 6 hourly) IV or oral
	Regular ibuprofen 400 mg TDS orally if tolerating oral fluids, without renal impairment or NSAID sensitive asthma.
	When PCA ceased, tramadol 50 - 100mg 4 hourly prn.
Oral intake	Diet as tolerated from 4 hours post operation. Protein drink at 4 hours post op and BD until eating and drinking well.
Antiemetic	Regular ondansetron 4mg IV BD from Day 1, droperidol IV PRN.
Mobilisation	Sit out of bed at 6 hrs post op if practical. Mobilise on Day 1 including shower and walk.
IV therapy	Titrate to euvolemia and normalised electrolyte levels. Cease as soon as possible when drinking equivalent volume.
VTE prophylaxis	TEDS, 5000 units heparin SC BD
IDC removal	Day 1 postoperation
Discharge	Aim for day 3.

2.4.2.2 Anaesthesia

All patients received standardised anaesthesia. Induction was achieved with a titrated dose of propofol and neuromuscular blockade, with reversal at discretion of the anaesthetist. Maintenance was achieved with oxygen, air and volatile anaesthetic with avoidance of nitrous oxide.

Intraoperatively, patients received 1g paracetamol, 40 mg parecoxib, 100 mg tramadol unless contraindicated by concurrent use of selective serotonin reuptake inhibitor (SSRI), and titrated intravenous fentanyl.

For PONV prophylaxis patients were given 4-8mg dexamethasone and either 4mg ondansetron, 2mg tropisetron or 1mg granisetron. If required during the post-anaesthesia recovery period further dexamethasone or ondansetron, or 0.5mg droperidol was given.

Avoidance of the use of ketamine, dexemetomedine and clonidine were encouraged due to the analgesic implications of these medications.

Active warming was achieved with warm air blanket.

Intravenous fluids were titrated to euvolemia. Colloid, Albumin, or Red blood cells were given if required.

When required, hypotension was managed with titrated metaraminol or ephedrine.

Antibiotic prophylaxis was routinely provided.

2.4.2.3 Surgery

All patients underwent colectomy by surgeons in an accredited Colorectal Surgery Unit at either the Royal Adelaide Hospital, St Andrew's Hospital or Calvary North Adelaide Hospital. Technical aspects of the surgical procedures separate to the intervention were determined at the discretion of the operating team.

Prior to skin closure the abdominal wall wounds were infiltrated with 20ml 0.2% Ropivacaine.

2.4.2.4 Intervention

On the basis of systematic review of the efficacy and safety of intraperitoneal ropivacaine for postoperative analgesia described in the literature review of this thesis, we have determined a dosing regimen of intraperitoneal instillation of 50ml 0.2% ropivacaine (100mg), both pre-dissection and end-surgery, followed by infusion via On-Q Painbuster at 10ml/hr (20mg/hr) for 48h, with a local wound infiltration (field block) to the abdominal wall incision at end-surgery of 20 ml 0.2% ropivacaine (40mg) will be optimal to potentially produce a clinical reduction in postoperative pain and yet to be below the threshold for clinical toxicity.

Therefore, on entry into the abdominal cavity and prior to dissection a 50 ml loading dose of either Control (0.9% saline) or IPLA (0.2% Ropivacaine) solution was instilled throughout the abdomen to coat the abdominal viscera and paracolic gutters. Suction or packs to excess moisture was avoided. Post-operation but prior to closure of abdominal wall a further 50 ml of Control (0.9% saline) or IPLA (0.2% Ropivacaine) solution was instilled throughout the abdomen to coat the operative region of greatest dissection. An ON-Q Painbuster (ON-Q Painbuster, B. Braun Melsungen AG, Melsungen, Germany) soaker catheter was passed through the abdominal wall in the relevant upper quadrant and placed intraperitoneally along the paracolic gutter corresponding with the region of greatest operative dissection, into the pelvis. The external end was fixed to the skin with dressing. After closure of the abdominal wall the external tubing end was connected to the continuous infuser reservoir and an intraperitoneal infusion of Control (0.9% saline) or IPLA (Ropivacaine, 20mg/hr) solution commenced immediately post-operation and continued for 48 hrs.

2.4.2.5 Standardised Adjunct Postoperative Analgesia

All patients received 1g regular paracetamol (acetaminophen) every 6 hours IV or orally (4g/day) until discharge. A patient-controlled analgesia pump (PCA) containing Fentanyl 1mg in 50ml 0.9% saline (20mcg/ml) was commenced immediately postoperatively providing boluses of 20 mcg available at 5min lockout intervals for patients < 70 years of age and 10 mcg at 5 min lockout intervals for patients > 70 years of age. This was managed and ceased at the discretion of the anaesthetists involved in the RAH Acute Pain Service, or the responsible clinical decision maker for patients of St Andrews Hospital or Calvary North Adelaide Hospital.

2.4.3 SPECIFIC SAFETY CONSIDERATIONS

2.4.3.1 The Risk for Ropivacaine Toxicity

Severe to life threatening side effects reported for Ropivacaine (Table 2.2) are similar to those observed with similar other local anaesthetics. These may result from overdosage, accidental intravenous injection, or altered absorption or metabolism of the drug.

Table 2.2: Side Effects of Ropivacaine

Side Effects	**Symptoms**	**How often is it likely to occur?**	**How severe might it be?**	**How long might it last?** (If symptoms related to the drug and the drug is stopped)
Nervous system	Decreased sensation of other body parts, fever or chills, headache, dizziness	> 1%	Mild	2 - 4 hours
	No sensation of other body parts	≤ 1%	Mild	
Heart	Low blood pressure	> 10 %	Moderate	2 - 4 hours
	Slow heart rate, high blood pressure and fast heart rate	> 1 %	Moderate	
Gastrointestinal	Nausea	> 10 %	Mild	2 - 4 hours
	Vomiting	> 1 %	Mild	
Other	Urinary retention	> 1 %	Moderate	2 - 4 hours
	Anxiety	≤ 1%	Mild	
Toxicity	Tingling of numbness of mouth and tongue	Unlikely as we will use a dose shown to be below the levels required to develop toxicity	Severe *Life threatening These symptoms appear in order and therefore there are reversible minor signs of toxicity present before serious problems occur. If you report these symptoms your treatment will be discontinued.	15-25min
	Inability to properly form words while speaking			
	Light-headedness			
	Visual and hearing disturbances			
	Muscle twitching			
	ECG changes			
	Cardiac arrest*			
Allergy	Anaphylaxis	Rare	Severe – Life threatening	Variable
	Cardiac arrest			

2.4.3.2 Clinical Monitoring for Ropivacaine Toxicity : Ropivacaine Toxicity Screening Chart

The surgical/anaesthetic team and other ward-based staff monitored participants for signs of side effects of ropivacaine as part of their standard management, as follows:

- The patient was under the direct care of an anaesthetist in the controlled monitored environment of operating theatre, with constant real-time respiratory and cardiac monitoring, while receiving supplemental oxygen at the time of intraperitoneal bolus instillation and commencement of infusion of ropivacaine.
- During the immediate post-operative period the patient was cared for in the Post-anaesthesia Recovery Unit (PARU) by 1:1 specialist nursing staff, with ongoing monitoring of respiratory and cardiac function, and supplemental oxygen.
- At all times in theatre and PARU the 1:1 ratio of specialist staff:patient allowed for direct observation of CNS toxicity manifested as perioral muscle twitching.
- If signs or symptoms of toxicity developed while in theatre or PARU then management plan was to cease ropivacaine administration, provide ongoing monitoring of the patients respiratory and cardiac function, and at the anaesthetists discretion, provide an intravascular lipid emulsion, known to counteract the toxic effects of ropivacaine.

- During the intermediate post-operative period the patient was cared for in a ward setting by trained nursing staff. A study information sheet was maintained in the front of the case file for each participant (Appendix 6.5). Screening for signs and symptoms of clinical toxicity occurred at intervals by assessment of vital signs: pulse, BP, RR, SaO_2, temperature, and use of a tool designed specifically for this study, the Ropivacaine Toxicity Screening Chart

(Appendix 6.6). This tool prompted nursing staff to ask the participant if they were experiencing one of the following symptoms of ropivacaine toxicity:

- Do you feel lightheaded?
- Have you experienced any numbness or tingling of your mouth or tongue?, and
- Have you noticed any muscle twitching?

- Ward-based nursing staff were instructed to respond to abnormal vital signs as per the clinical chart guidelines. If a patient provided a positive response to any of the ropivacaine toxicity screening questions then ward-based nursing staff were advised to pause the infusion and initiate a medical officer review. If nursing staff directly observed muscle twitching they were instructed to initiate a Medical Emergency Response (MER) call for immediate medical officer review. At any time, if a medical officer suspected that the sign or symptom was the result of ropivacaine infusion, the infusion was immediately ceased and further investigation and management implemented, such as transfer to a monitored bed. The principal investigator was notified of the event during business hours, and provided a report regarding the event to the IDSC/HREC within 48 hours of occurrence

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All the staff involved in care of the study patients were educated to provide the care as described above and an information sheet for staff was made available in the case-notes for each study participant.

2.4.3.3 Risk for Infusion Catheter-Associated Infection

The use of an infusion device is associated with a low risk of catheter associated infection. If this happens, it can be easily treated. The surgical team monitored participants for signs of infection as part of their normal management.

2.4.3.4 Safety Monitoring

At a minimum of monthly the principal investigator conducted interviews with the Colorectal Surgeons and Anaesthetists performing bowel surgery for the participants to ensure there were no concerns regarding the safety of the experimental infusions.

A monthly audit of all postoperative complications and side effects of ropivacaine that occurred within a 30d postoperative period was performed and reported at the Study Working Group Meetings.

During the hospital inpatient stay and at the completion of involvement with the research project participants were invited to give verbal feedback on the project. Feedback was not restricted to these times.

The severity of adverse effects associated with ropivacaine are defined in the Table 2.2. Severe to life threatening side effects of ropivacaine were reported to the Chairman of the Research Ethics Committee within 72 hours of occurring.

2.4.3.5 Stopping Criteria

Stopping rules for the study included:

- The occurrence of symptoms and signs of toxicity from ropivacaine infusion, which are suspected by a medical officer to be directly attributable to use of the drug, in two patients.
- The occurrence of anaphylaxis or cardiac arrest during ropivacaine infusion, which is suspected by a medical officer to be directly attributable to allergy to ropivacaine, in two patients.

2.4.4 WITHDRAWAL CRITERIA

A participant was withdrawn from the research project if they

I. withdrew consent prior to commencement of the intervention,

II. required a significant deviation from standardised anaesthetic protocol or required intraoperative insertion of abdominal drain.

No data from a withdrawn participant was included in statisitical analysis.

The intervention was stopped if the participant

I. developed a Painbuster catheter associated infection,

II. developed a side effect of ropivacaine infusion (See SAFETY SPECIFIC CONSIDERATIONS for full list), which was suspected by a medical officer to be directly attributable to use of the drug, and was incompatible with patient safety or intolerable to the patient.

Data collection was continued and analysed in an intention-to-treat basis.

Participant data collection was ceased if they

I. withdrew consent following commencement of the intervention,

II. required a significant deviation from standard postoperative recovery including an unplanned return to theatre, or commencement of chemoradiotherapy during the 45 day follow up period.

Data collected up to the time of cessation was included in statistical analysis.

2.4.5 CLINICAL STAFF CREDENTIALLING AND TRAINING

All clinical staff involved in this study complied with the accreditation and credentialing requirements of their clinical role as outlined by either The Royal Adelaide Hospital, St Andrews Hospital or Calvary North Adelaide Hospital, and in accordance with state and federal law.

All site staff with allocated responsibilities or tasks in the study, particularly surgeons, anaesthetists and ward-based staff, received study protocol training, and training regarding the investigational product, recognition of clinical toxicity, safety reporting systems and protocol for unblinding in the event of risk to the patient. Attendance at training was recorded on a sign-in attendance sheet. Any questions raised during the training, including responses, were documented and filed by the principal investigator. A copy of training material was maintained on file. Compliance with the study protocol was audited by the principal investigator at regular intervals.

2.5 ETHICAL CONSIDERATIONS

2.5.1 RESEARCH PARTICIPANTS

The National Statement identifies the need to pay attention to ethical issues associated with research involving specific populations. In this study, information regarding a participants' nationality or cultural background was not sought, therefore Aboriginal and/or Torres Strait Islander peoples may have been coincidentally recruited to the study. The study exclusion criteria, including "Inability to consent or complete data scores in the study questionnaires due to cognitive impairment and/or language barrier" aims to protect vulnerable individuals from any cultural background. Consent was sought with the customs and requirements of each individual participants' community taken into consideration, adhering to the NHMRC guidelines for Ethical Conduct and Aboriginal and Torres Strait Islander Health Research.

In this study people who may have been involved in illegal activity may have been coincidentally recruited to the study as it is not always possible for researchers to be able to know who is and is not. In the current study the researchers adhered to their legal responsibilities as members of the community and clinicians.

2.5.2 RELATIONSHIP OF INVESTIGATORS TO PARTICIPANTS

This is defined as the Patient-Doctor relationship. The participants were patients being treated at either The Royal Adelaide Hospital, St Andrews Hospital or Calvary North Adelaide Hospital, and highly dependent on medical care. This relationship should not have influenced a patient's decision making regarding study participation. Refusal to take part in the study did not involve penalty or loss of benefits or attention to which they were otherwise entitled to receive from their health care provider. Participants were informed they were free to decide at any time that they no longer wish to participate in the trial and that leaving the trial will not affect their future treatment. They were also assured that leaving the trial will not have any negative effect(s) on their relationship with the treating doctor or the hospital staff. This information is and was clearly stated in the Participant Information Sheet.

2.5.3 PRIVACY / CONFIDENTIALITY

Information collected directly from the participant was individually identifiable as it made up part of their hospital medical record. This was required in order to ensure a complete medical history is maintained by the hospital for future medical care. All trial personnel reviewing the patient's information were familiar with Australia's laws on confidentiality and privacy and their employment contract includes a mandate to uphold those laws. Deidentified information collected about participants was analysed as group data to test the hypotheses defined in the study protocol. The results of this analysis will be published in a peer-reviewed journal.

2.5.1 THE PARTICIPANTS' EXPERIENCE DESCRIBED IN LAYMANS TERMS

Participants received the standard care of persons having bowel surgery at the Royal Adelaide Hospital. In addition to the standard post-operative pain relief regimen that included a Patient Controlled Analgesia (PCA) pump for self-administration of opioid, the participant also had a thin catheter inserted into the abdomen while anaesthetised. It was fixed to the skin to avoid accidental removal and connected to an infusion device called a "painbuster", about the size of a tennis ball, which was carried using a small carry-bag. This device administered the continuous infusion of Ropivacaine or Saline and was removed after 48hrs.

Participants completed a diary prompting provision of a score reflecting their level of pain, and recovery at intervals post- operation. They also recorded details such as first drink, food, and first flatus.

The trial coordinator visited the participants while in hospital to ensure their comfort and progress. Following discharge, participants were contacted by the trial coordinator to determine satisfaction with participation and to gain further scores of pain, and recovery up to day 45 post-operation.

2.6 OUTCOMES

2.6.1 BASELINE PATIENT DATA

The baseline patient data recorded was age, sex, BMI, past medical history, past surgical history, American Society of Anesthesiologists (ASA) score, and Colorectal Physiological and Operative Severity Score (Cr-POSSUM) [135].

Perioperative data to be recorded was operation performed, operation time, intraoperative adherence to anaesthetic protocol, intraoperative intravenous fluid use, and intravenous fluid administered within the first postoperative 24hours.

2.6.2 PRIMARY OUTCOME MEASURE – SURGICAL RECOVERY SCALE

The postoperative domains of recovery of fatigue, and the post-discharge return to normal functioning in both cognition (concentration) and activities of daily living were assessed using the Surgical Recovery Scale (SRS) [68] pre-operatively (baseline) and on postoperative days 1, 3, 7, 30 and 45. This was administered in the form of a patient diary (Appendix 6.7) Once discharged from care the patient diary with instructions was returned by email or mail with a phone call or email reminder.

2.6.3 SECONDARY OUTCOME MEASURES

2.6.3.1 Pain – Visual Analogue Score

Postoperative pain at rest was evaluated using a 100mm Visual Analogue Scale with the end-points labelled “no pain” and “the worst possible pain”[78] [79] for each of:

I. somatic pain (incisional pain in the abdominal wall that the patient can touch)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain

at postoperative hours 3, 6, 12, 24, 48, and 72, and at day 7. This was administered in the form of a patient diary (Appendix 2.5) Once discharged from care the patient diary with instructions was returned by email or mail with a phone call or email reminder.

2.6.3.2 Total Adjunct Opioid Use

Total opioid analgesia use during the postoperative day 1, 2, and 3 prior to discharge was recorded and quantified using the Mean Equivalent Dose (MED) method[136-140]. Initially this was parenteral fentanyl consumption, as part of the pain protocol in PACU and recorded daily in the PCA device

until removal of PCA. Thereafter, prn tramadol, ibuprofen, or other opioid use as charted, until discharge. The use of rescue ketamine infusion was not included in the study protocol, but was noted to be prescribed by clinicians when very high doses of parenteral opioids were consumed. If a patient was provided with an additional ketamine infusion for rescue analgesia this was recorded.

2.6.3.3 Recovery of Normal Bowel Function

In the current study the following indicators of return of normal bowel function were recorded: time to tolerating oral fluid, oral diet and to first postoperative flatus, and bowel motion. A diagnosis of ileus was made on clinical findings or the requirement for insertion of naso-gastric tube. Ileus manifests clinically with nausea, vomiting, intolerance of food and fluid and therefore a requirement for intravenous fluid therapy and naso-gastric tube placement. In the current study post-operative antiemetic use was recorded, as were number of episodes of vomiting. The length of time requiring postoperative intravenous fluid was recorded.

2.6.3.4 Time to Readiness For Discharge (TRD)

TRD and actual length of stay (LOS) were recorded. Readmission, defined as unplanned return to hospital within 30d surgery and requiring an overnight admission, was recorded.

2.6.3.5 Operative Complications

All complications that occurred within a 30d postoperative period were recorded and graded using the Clavien-Dindo classification system[141 142]

Table 2.3: Classification of Surgical Complications[141 142]	
Grade	**Definition**
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III Grade IIIa Grade IIIb	Requiring surgical, endoscopic or radiological intervention. Intervention not under general anesthesia Intervention under general anesthesia
Grade IV Grade IVa Grade IVb	Life-threatening complication (including CNS)* requiring IC/ICU management. Single organ dysfunction (including dialysis) Multiorgan dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.
*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.	

2.7 STATISTICAL ANALYSIS

Patient recruitment and flow are reported and represented in CONSORT diagram (Figure 3.1). Data was analysed as a cohort analysis of all participants with subgroup analysis of participants in the laparoscopic arm only.

Data was assessed for normality using the Shapiro-Wilk test. Skewed data sets including time to oral fluid, diet and first flatus were log transformed. Results are presented as either Mean ± SEM or Median (Interquartile Range, IQR) for parametric data, or Geometric Mean (95% Confidence Interval, CI) for log-transformed parametric data. Differences in categorical variables was determined using the Fisher's Exact or Pearson's chi-square test, while differences in ordinal variables was determined via a Mann-whitney U Test for ordinal variables, and student's T-test for parametric variables as indicated. The SRS score at baseline and each postoperative time-point was compared between IPLA and Control groups, in accordance with validated design[68], and the change in SRS across time was not tested. A negative binomial regression was used to determine a statistical difference in incidence of vomiting episodes, presented as Incidence Rate Ratio (95% CI). All analyses were performed using Stata14 (StataCorp LP, College Station, TX). Statistical significance was accepted at $P < 0.05$.

3. RESULTS

3.1 Participant Recruitment and Flow

3.1.1 RECRUITMENT TIMELINE

Between May 2015 and July 2016, 180 patients were screened for inclusion at the Royal Adelaide Hospital. Recruitment at St Andrew's Hospital occurred between August 2015 and July 2016, and at Calvary North Adelaide Hospital between November 2015 and July 2016.

3.1.2 PARTICIPANT FLOW

180 individuals were identified as potential participants. 30 declined to participate. Of the remaining individuals 107 were eligible to participate according to the criteria outlined in Section 2.1. 90 participants were randomized equally between the Control and IPLA groups. See Figure 3.1 for CONSORT Diagram.

Five participants in the control group and three in the IPLA group noted accidental removal of painbuster catheters prior to completion of the 48hr infusion. One participant in the control group and three in the IPLA group had painbuster catheters removed early due to clinical suspicion of ropivacaine toxicity (see Section 3.4.1 for details). Two participants in the IPLA group were noted to have incomplete emptying of painbuster pump reservoirs. All of the above patients were analysed on an intention to treat basis. The number of SRS questionnaires that were not completed was: 1,3, 23, 27, 20 and 19 for baseline, postoperative day 1, 3, 7, 30 and 45, respectively. Noncompletion rates were similar between IPLA and control groups, resulting from participant noncompliance, loss to follow up, or withdrawal from data collection according to the criteria outlined in Section 2.4.5. All individual items achieved a minimum of 70% completed data.

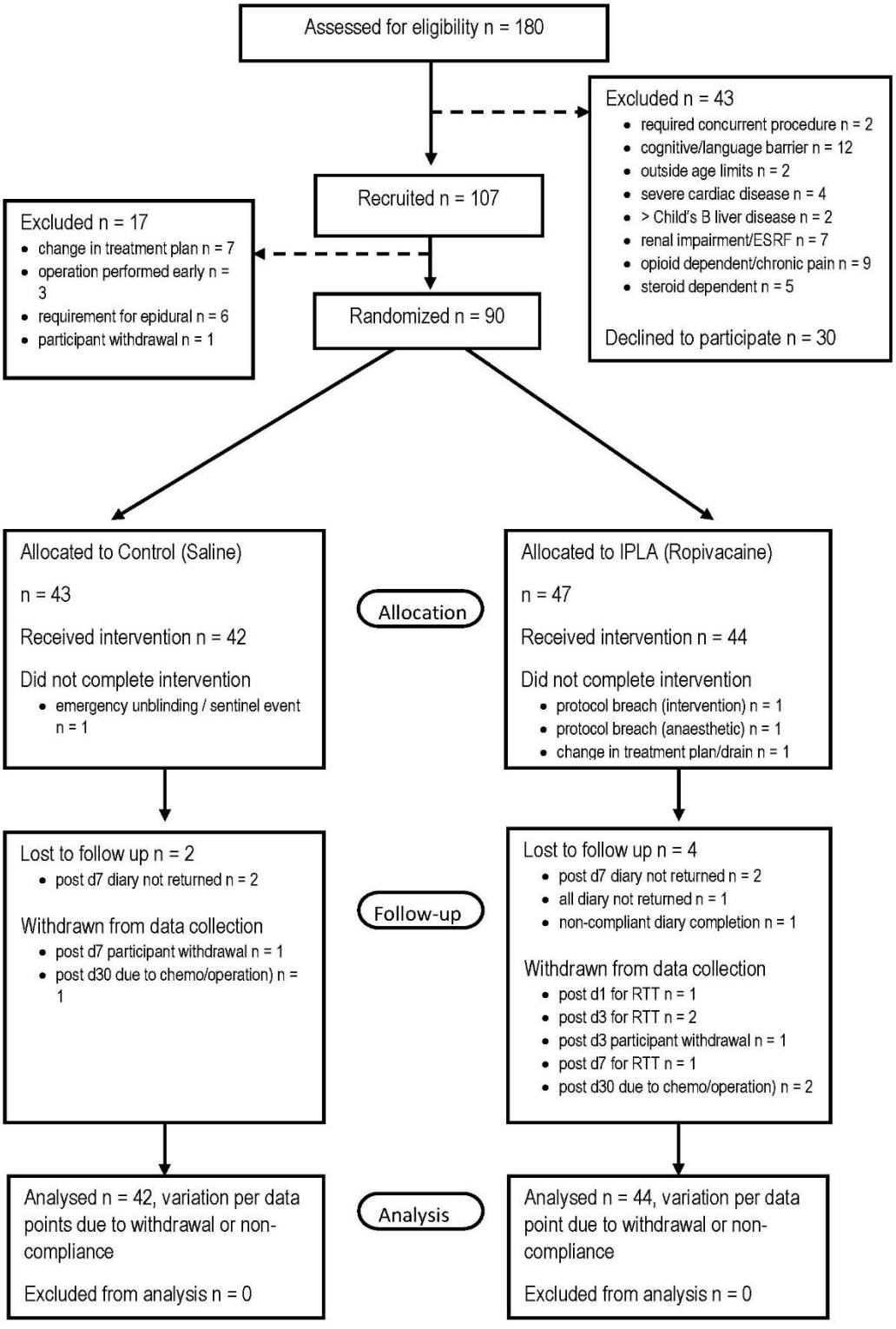


Figure 3.1 CONSORT Diagram of Participant Flow

The number of participants who were randomly allocated, received the study intervention, and were analysed for outcome measures in the Control and IPLA groups.

3.1.3 LOSSES AND EXCLUSIONS AFTER RANDOMISATION

Four participants (Control = 1, IPLA = 3) were excluded after randomization due to: intraoperative change in management requiring insertion of abdominal drain (open arm, IPLA group); emergency unblinding in response to intraoperative critical event (lap arm, control group; See Section 3.4.2 – Emergency Unblinding Event – Severe Adverse Event for details); and significant deviation from study protocol including one participant (open arm, IPLA group) who did not receive the study intervention due to surgeon omission of intraoperative intraperitoneal bolus doses and incorrect preparation of painbuster by theatre staff, and one participant (open arm, IPLA group) to whom the anaesthetist administered 147.25 mg iv lignocaine over 20min and 3.12mg ketamine intraoperatively. These participants did not have study data collected and were not included in analysis.

3.2 Baseline Data

The baseline patient and perioperative data were similar between the Control and IPLA groups (Table 3.1)

Table 3.1: Baseline patient and perioperative data

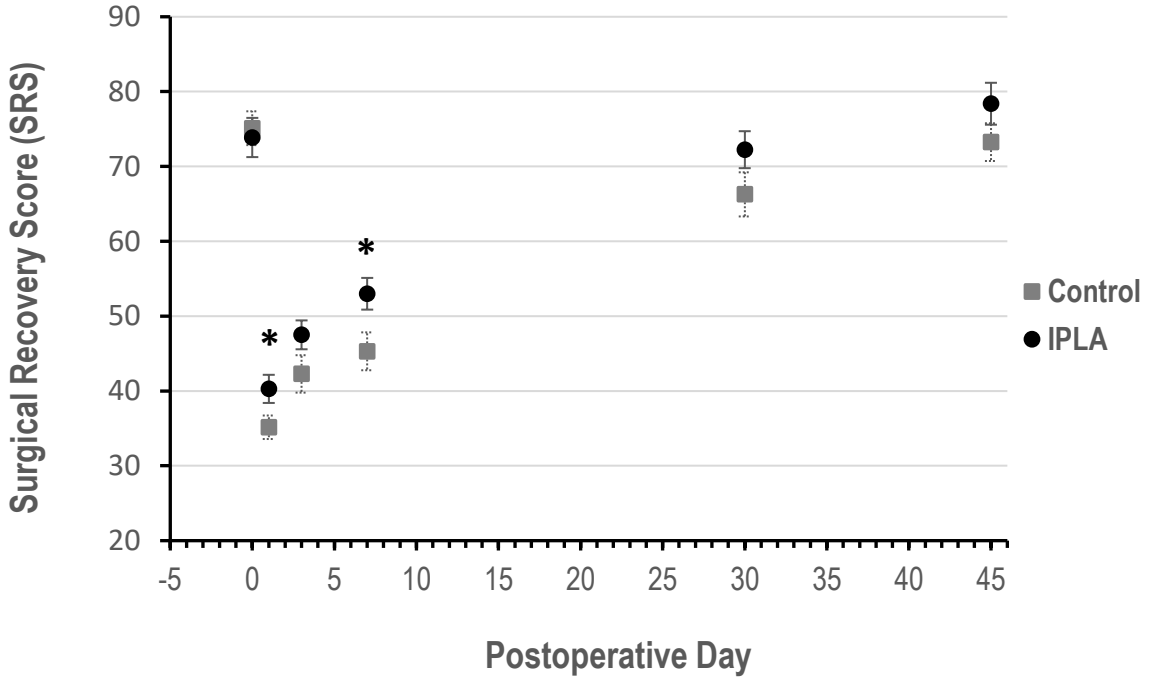
	All Participants (n=86)		Subgroup Laparoscopic Approach (n=51)	
	Control (n=42)	IPLA (n=44)	Control (n=25)	IPLA (n=26)
Surgical Approach				
Open	14 (33.3%)	13 (29.5%)		
Lap conversion to open	3 (7.1%)	5 (11.4%)		
Laparoscopic	25 (59.6%)	26 (59.0%)	25 (49%)	26 (51%)
Age (median in yrs, IQR)	63.4 (54.4, 72.4)	67.9 (59.4, 76.4)	63.2 (54.8, 71.3)	71.4 (60.7, 77.3)
Gender				
Female	22 (52.4%)	18 (40.9%)	11 (44%)	11 (42.3%)
Male	20 (47.6%)	26 (59.1%)	14 (56%)	15 (57.7%)
BMI (mean in kg/m^2, SD)	26.4 ± 5.6	28.6 ± 2.9	26.4 ± 4.8	28.5 ± 4.5
ASA				
I	2 (5%)	0 (0%)	2 (8.3%)	0 (0%)
II	30 (75%)	26 (66.7%)	16 (66.7%)	16 (72.7%)
III	8 (20%)	13 (33.3%)	6 (25%)	6 (27.3%)
Cr-POSSUM (median % risk, IQR)	1.85 (0.92, 2.51)	1.85 (1.30, 2.60)	1.85 (0.90, 2.58)	1.9 (1.33, 2.60)
Diagnosis				
Polyp / cancer	30 (73.2%)	28 (66.6%)	22 (88%)	20 (83.3%)
Diverticulitis	6 (14.6%)	7 (16.7%)	0 (0%)	1 (4.2%)
IBD	4 (9.8%)	5 (11.9%)	2 (8%0	2 (8.3%)
Other benign	1 (2.4%)	2 (4.8%)	1 (4%)	1 (4.2%)
Operation time (median in min, IQR)	165 (130, 180)	150 (121, 190)	167 (130, 190)	153 (135, 190)
IVT (mean in ml ± SD)				
Intraoperative	1694 ± 676	1674 ± 775	1759 ± 633	1654 ± 750
First Postoperative 24hr	2975 ± 649	3081 ± 1068	2924 ± 700	2927 ± 874

N indicates number of patients; IQR, interquartile range; BMI, body mass index; SD, standard deviation; Cr-POSSUM, Colorectal-Physiological and Operative Severity Score for the enumeration of postoperative morbidity and mortality.

3.3 Postoperative Surgical Recovery and Pain Outcomes

3.3.1 COHORT ANALYSIS OF ALL PARTICIPANTS N=86

When considering the SRS scores at each postoperative time-point for the IPLA and Control groups, participants in the IPLA group were shown to have an improved functional recovery at postoperative day 1 and day 7 compared with Control (Figure 3.3.1). Participants in the IPLA group scored significantly lower on VAS for somatic pain at postoperative 3, 6, 12 and 24h, and on VAS for visceral pain at postoperative 3, 12, 24h and 7days. The mean shoulder tip pain score was less than 8mm with SEM < 4mm for every time point assessed, and not different between the groups. There was a trend (P=0.08) toward reduced opioid use (MED) in the IPLA group during the first 24hr post operation (Table 3.2), but no significant difference between IPLA and control in opioid use (MED) during postoperative day 2 or day 3. The data for these two items was skewed requiring log-transformation and is therefore not presented in table form. There was a significant difference in the incidence of the introduction of rescue ketamine infusion between the groups, with rescue ketamine used for six Control participants, in contrast with one IPLA participant. Participants in the IPLA group passed flatus 10h earlier than their Control counterparts and there was also a trend towards an earlier bowel motion. There was no difference in the time to first oral fluid or food intake. There was a nonsignificant 14.1% decrease in the number of vomiting episodes in IPLA participants and no difference in rate of ileus between the Control and IPLA groups. The TRD, LOS complication rate, and anastomotic leak rate were not different between the groups (Table 3.3).



	Number of participants analysed, n					
	SRS Baseline	SRS day 1	SRS day 3	SRS day 7	SRS day 30	SRS day 45
Control	42	41	30	29	32	33
IPLA	43	42	33	32	34	34

Figure 3.2 Postoperative recovery following colectomy by any approach

Surgical Recovery Score at baseline (Day 0, preoperation), and following colectomy to postoperative day 45 for the Control (normal saline) and IPLA (intraperitoneal local anaesthetic) groups. Data is presented as Mean ± SEM. * $P < 0.05$.

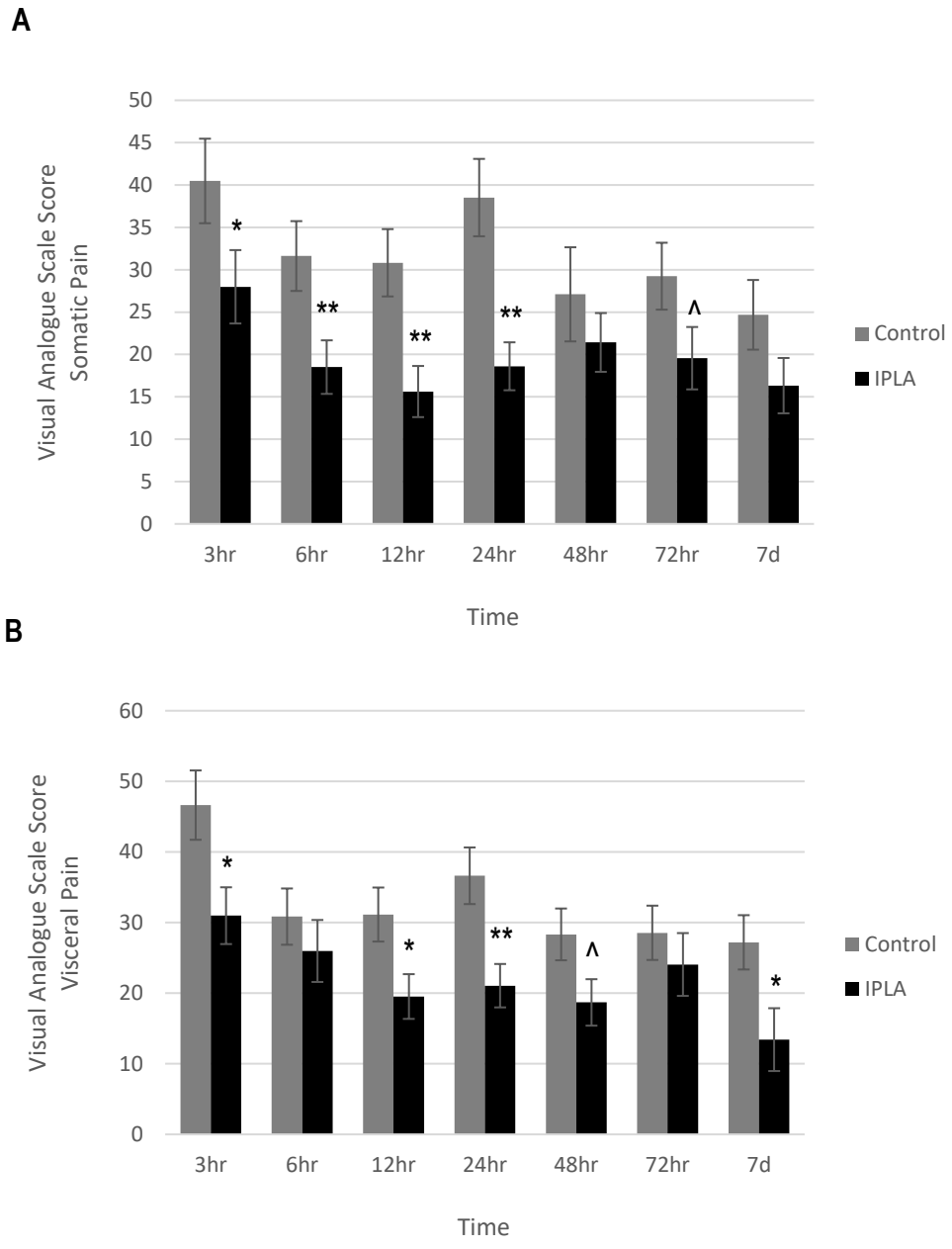


Figure 3.3 Visual Analogue Scale Pain Scores - Post Colectomy

Visual analogue scale pain score for (A) somatic pain and (B) visceral pain at rest following colectomy by any approach from postoperative 3 hours to day 7 for the Control (normal saline) and IPLA (intraperitoneal local anaesthetic) groups. Data is presented as Mean ± SEM. ** $P < 0.01$, * $P < 0.05$, ^ $P < 0.08$.

Table 3.2: Recovery of Bowel Function, Discharge Parameters and Complication Rates following Colectomy

	Control		IPLA		P value
Return of Bowel Function (g-mean in hours [CI])	(n)		(n)		
Time to oral fluid	42	8 [7, 10]	43	10 [7, 12]	0.39†
Time to diet	41	24 [18, 31]	41	21 [17, 25]	0.41†
Time to flatus	39	45 [38, 52]	39	34 [28, 41]	0.03†
Time to bowel motion (mean)	40	91 [74, 104]	39	75 [61, 89]	0.09†
Number of vomiting episodes (IRR, CI)	42	0.86 [0.36, 2.05]	44	0.60 (0.32, 1.09)	0.73◊
Diagnosis of ileus	42	10 (24%)	43	5 (11%)	0.14‡
Discharge Parameters (median in days, IQR)					
TRD	41	4.5 [3.0, 5.9]	41	3.7 [2.8, 5.5]	0.20╫
LOS	42	6.0 [4.7, 9.0]	41	5.5 [4.0, 6.9]	0.20╫
Opioid Use (mean in MED± SEM)					
Post operative day 1	42	91.4 ± 9.6	44	72.9 ± 9.3	0.08╫
Post operative day 2	42		44		
Post operative day 3	42		44		
Use of rescue ketamine infusion	42	6 (14%)	44	1 (2%)	0.05♦
Readmission rate	42	2 (5%)	44	5 (11%)	0.61‡
Complication rate	42	15 (36%)	44	14 (32%)	0.82‡
Complication type	42		44		
Wound dehiscence		0		1	
Urinary retention		0		1	
Respiratory infection		3		3	
Anastomotic leak		1		4	
Intraperitoneal collection		2		1	NS
Bacteremia (no leak)		1		1	
Cardiorespiratory		1		3	
Bleeding		3		0	
Other		2		1	
Complication grade (Clavien-Dindo)	42		44		
I		13		9	
II		3		5	
III		3		5	NS
IV		3		3	
V		0		0*	

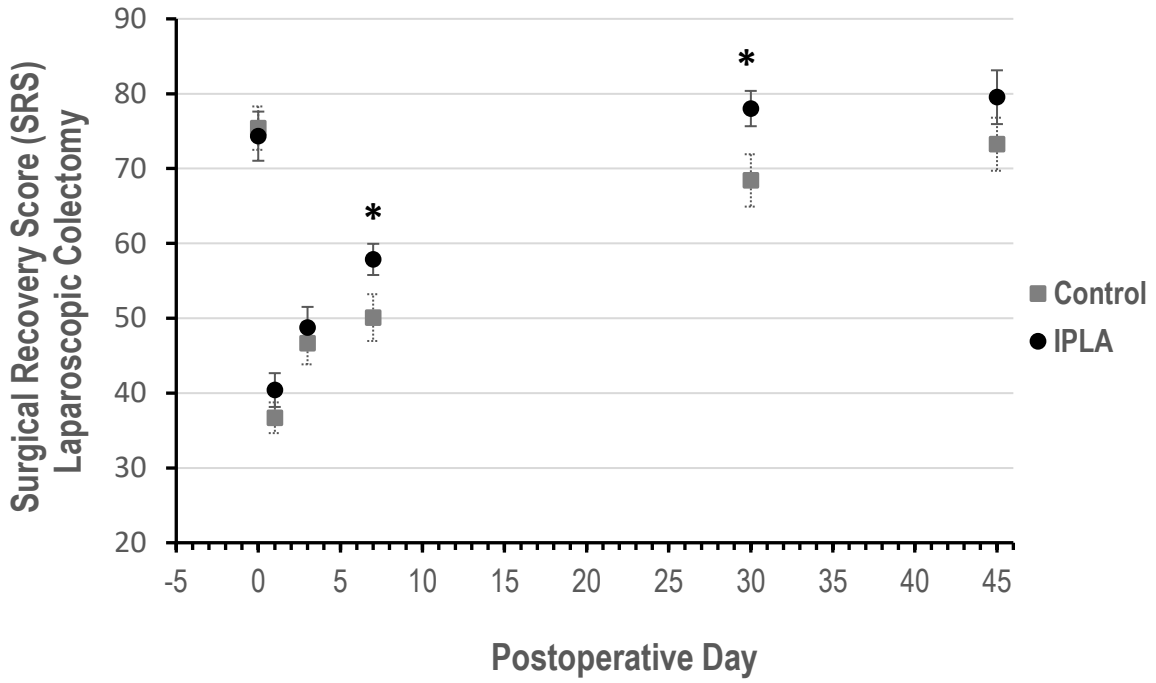
N indicates number in group; n indicates number analysed; g-mean, geometric mean; CI, 95% confidence interval; IRR, incidence rate ratio; IQR, interquartile range; TRD, time to readiness for discharge; LOS, length of stay; MED, milliequivalent dose; SEM, standard error of the mean.

*patient death related to initial operation and complication but > 30 days post operation.

† student's t-test, ‡ Pearson chi-square, ◊negative binomial regression, ╫Mann-Whitney, ♦Fisher's exact

3.3.2 SUBGROUP ANALYSIS OF LAPAROSCOPIC PARTICIPANTS N=51

When considering the SRS scores at each postoperative time-point for the IPLA and Control groups of participants who underwent surgery by the laparoscopic approach, participants in the IPLA group were shown to have an improved functional recovery at postoperative day 7 and day 30 compared with Control (Figure 3.3.4). Participants in the IPLA group scored significantly lower on VAS for somatic pain at postoperative 3, 6, 12, 24h, and 7 days and on VAS for visceral pain at postoperative 3, 12, 24, 48h and 7days. The mean shoulder tip pain score was less than 12 mm with SEM < 8 mm for every time point assessed, and not different between the groups. There was a trend ($P<0.09$) toward reduced opioid use (MED) in the IPLA group during the first 24hr (Table 3.3), but no significant difference between IPLA and control in opioid use (MED) during postoperative day 2 or day 3. The data for these two items was skewed requiring log-transformation and is therefore not presented in table form. There was no difference in the rate of rescue ketamine infusion between the groups. There was no difference in the time to first oral fluid, food intake, flatus or bowel motion. There was no difference in the number of vomiting episodes or rate of ileus between the Control and IPLA groups. The TRD, LOS complication rate, and anastomotic leak rate were not different between the groups (Table 3.3).



	Number of participants analysed, n					
	SRS Baseline	SRS day 1	SRS day 3	SRS day 7	SRS day 30	SRS day 45
Control	25	24	19	16	17	18
IPLA	26	26	18	21	21	22

Figure 3.4 Postoperative recovery following laparoscopic colectomy

Surgical Recovery Score at baseline (Day 0, preoperation), and following laparoscopic colectomy to postoperative day 45 for the Control (normal saline) and IPLA (intraperitoneal local anaesthetic) groups. Data is presented as Mean ± SEM. * $P < 0.05$.

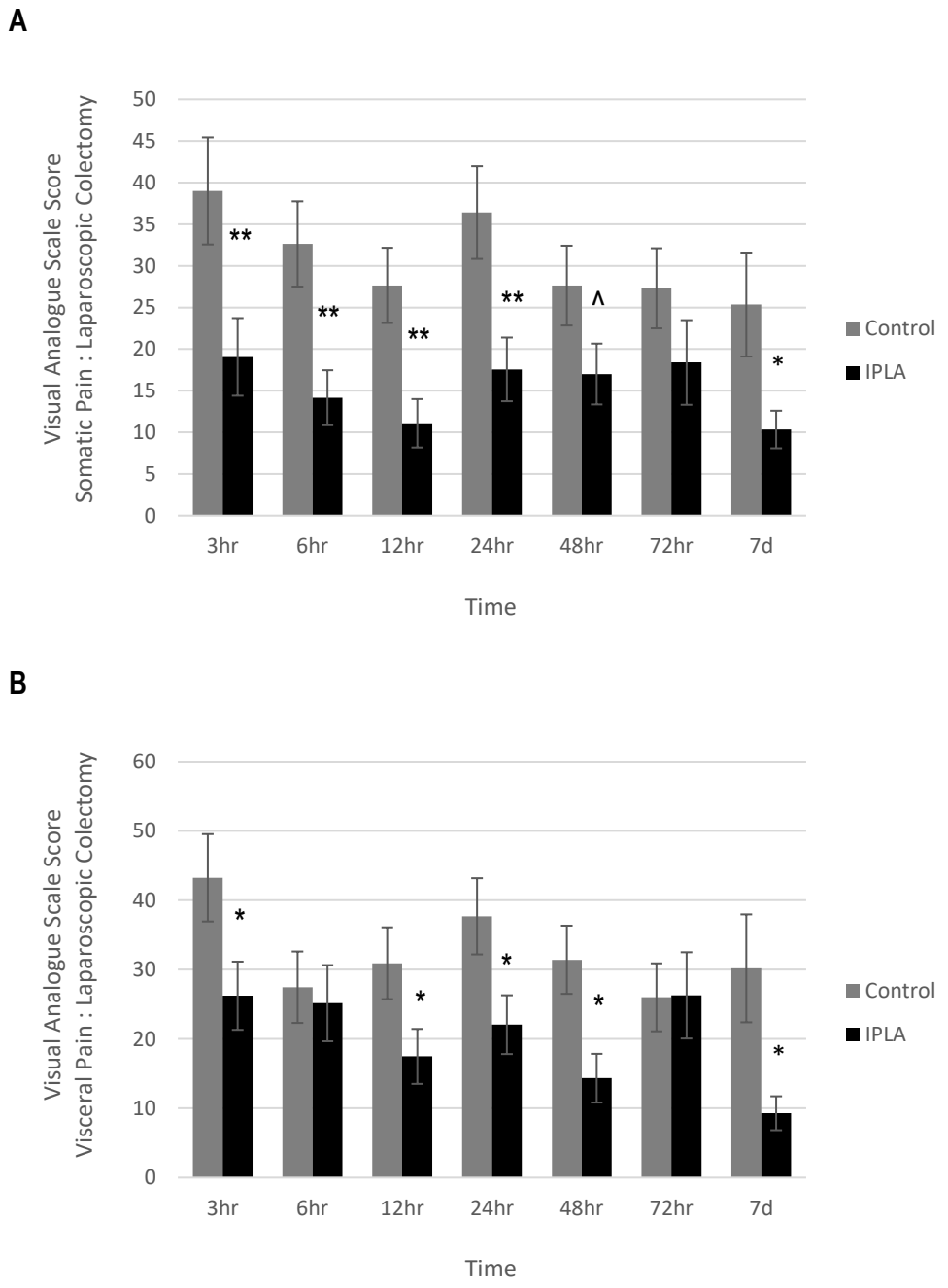


Figure 3.5 Visual Analogue Scale Pain Scores – Post Laparoscopic Colectomy

Visual analogue scale pain score for (A) somatic pain and (B) visceral pain at rest following laparoscopic colectomy from postoperative 3 hours to day 7 for the Control (normal saline) and IPLA (intraperitoneal local anaesthetic) groups. Data is presented as Mean ± SEM. ** $P < 0.01$, * $P < 0.05$, ^ $P < 0.08$.

Table 3.3: Recovery of Bowel Function, Discharge Parameters and Complication Rates following Laparoscopic Colectomy

	Control (N=25)		IPLA (N=26)		P value
Return of Bowel Function (mean in hours, CI)	(n)		(n)		
Time to oral fluid	25	9 [6, 10]	25	9 [6, 13]	0.58†
Time to diet	25	22 [15, 31]	23	18 [14, 24]	0.45†
Time to flatus	24	42 [34, 52]	26	33 [25, 42]	0.11†
Time to bowel motion (mean)	23	91 [78, 104]	22	75 [61, 90]	0.22†
Number of vomiting episodes (IRR, CI)	25	0.52 [0.29, 0.75]	26	1.07 [0.72, 1.42]	0.90◊
Diagnosis of ileus	25	4 (16%)	25	1 (4%)	0.16‡
Discharge Parameters (median in days, IQR)					
TRD	24	3.8 [2.4, 5.2]	25	3.0 [2.5, 3.9]	0.29╫
LOS	24	5.0 [4.0, 6.1]	25	5.1 [3.6, 6.6]	0.53╫
Opioid Use (mean in MED, SEM)					
Post operative day 1	25	68.0 (7.59)	26	52.7 (9.40)	0.09╫
Post operative day 2	25		26		
Post operative day 3	25		26		
Use of rescue ketamine infusion	25	3 (12.0%)	26	0 (0.0%)	0.11♦
Readmission rate	25	1 (4%)	26	1 (3.8%)	1.00‡
Complication rate	25	7 (28%)	26	6 (23%)	0.75‡
Complication type	25		26		
Respiratory infection		2		1	
Anastomotic leak		1		1	
Intraperitoneal collection		1		1	
Bacteremia (no leak)		1		1	NS
Cardiorespiratory		1		2	
Bleeding		1		0	
Other		0		1	
Complication grade (Clavien-Dindo)	25		26		
I		10		2	
II		1		2	
III		2		1	NS
IV		1		2	
V		0		0	

N indicates number in group; n indicates number analysed; g-mean, geometric mean; CI, 95% confidence interval; IRR, incidence rate ratio; IQR, interquartile range; TRD, time to readiness for discharge; LOS, length of stay; MED, milliequivalent dose; SEM, standard error of the mean.

† student's t-test, ‡ Pearson chi-square, ◊negative binomial regression, ╫Mann-Whitney, ♦Fisher's exact

3.4 Screening for Clinical Toxicity of Ropivacaine and Safety Measures

3.4.1 Ropivacaine Toxicity Screening Chart- Reported symptoms and action taken

The ropivacaine toxicity screening chart was completed for all participants and was locatable in the case notes of Control n=40 and IPLA n=43 participants. A subjective symptom(s) of clinical ropivacaine toxicity was reported by seventeen participants (Table 3.3). All participants had a normal blood pressure, pulse, and ECG unchanged from baseline at the time of reporting, except one participant shown to be in atrial fibrillation (AF), but with a normal QRS complex. There was no difference in the rate of symptom reporting between the Control and IPLA groups. The postoperative painbuster infusion was ceased early for four participants due to clinical concern. The participant with delirium did not improve significantly following cessation of painbuster infusion. The participant who reported blurry vision was reviewed by an ophalmologist on the ward who reported a previously undiagnosed visual defect requiring glasses for correction. The participant reporting perioral numbness improved 10min post cessation of infusion, with no alternate cause present, however the operation report commented on a clinical suspicion of undiagnosed liver disease, despite normal preoperative liver function tests. In the presence of undiagnosed liver disease there may be lower mean ropivacaine clearance as it is known that patients with end-stage liver disease have about a 60% lower mean ropivacaine clearance than healthy subjects and are thus expected to have over two-fold higher steady-state ropivacaine plasma concentrations during a continuous ropivacaine infusion[114]. For this participant perioral numbness was reported at 190 minutes following the second bolus dose, and It is therefore highly likely that clinical ropivacaine toxicity was identified.

For the participants (Control n = 3, IPLA n = 3) that were observed to develop arrhythymia an alternate cause was present in 100% of cases, including sepsis secondary to pneumonia or anastomotic leak, electrolyte disturbance secondary to high-volume lower GI losses, malabsorption of oral anti-arrhythymic agent secondary to ileus and critical bleed associated hypotension.

Table 3.4: Ropivacaine Toxicity Screening Chart – Reported Symptoms and Action Taken		
	Control (N=40)	IPLA (N=43)
Early removal of painbuster		
For delirium	1	0
For AF, subsequently explained by alternate cause	0	1
For perioral numbness	0	1
For blurry vision, subsequently explained by alternate cause	0	1
Painbuster intermittently clamped		
For lightheadedness	4	4
For lightheadedness, alternate explanation present	3	1
For muscle twitching	1	0
For muscle twitching, alternate explanation present	1	1

3.4.2 EMERGENCY UNBLINDING EVENT – SEVERE ADVERSE EVENT

In response to an intraoperative severe adverse event (SAE) a participant in the laparoscopic arm at Calvary North Adelaide Hospital was withdrawn from the study and had emergency unblinding of study group allocation performed. The SAE occurred approximately 2 minutes following abdominal insufflation with CO_2 and intraperitoneal instillation of experimental solution via laparoscopic port. The patient became bradycardic then recorded asystole. This was recognised by the anaesthetist to likely be a vagal response to laparoscopic insufflation therefore 2 minutes cardiopulmonary resuscitation (CPR) and 600mcg atropine were administered with reversion to normal cardiac activity. To allow for clarity in management the study protocol was abandoned and study group allocation unblinded to CONTROL (normal saline).

This SAE was conclusively not related to study intervention.

4. Discussion, Conclusions and Future Directions for Research

4.1 Summary

This is the first study to establish the effect of intraperitoneal local anaesthetic (IPLA) instillation and postoperative infusion on functional postoperative recovery following colectomy, in the absence of concurrent epidural analgesia. In this study participants underwent colectomy by both the open and laparoscopic approach and received optimised perioperative care within an ERAS program. The local anaesthetic drug ropivacaine was instilled into the intraabdominal space pre-and post-dissection during colectomy, and then infused into the intraperitoneal space during the first postoperative 48 hours. This technique resulted in an improvement in functional postoperative recovery, in the domains of fatigue, vigor, mental function, impact on patient activity and impact on ADLs, as assessed by the Surgical Recovery Scale (SRS). It also resulted in reduced pain scores for up to one week postoperation, as assessed by 100mm Visual Analogue Scale (VAS), a decreased need for rescue ketamine infusion analgesia, and an earlier passage of flatus.

4.2 IPLA Instillation and Infusion Improves Functional Postoperative Recovery Following Colectomy

Intraoperative instillation and postoperative infusion of IPLA following colectomy enhances functional recovery during the infusion period. In this study postoperative infusion of IPLA for 48 hrs resulted in an improved SRS score during the infusion, on day 1 postoperation. At day 3 postoperation, 24hrs after cessation of infusion, there was no persisting effect of IPLA on recovery. This is comparable with the key prior study by Kahokehr and colleagues[1], where augmentation of epidural analgesia with IPLA infusion for 72 hrs resulted in an improvement in SRS during the infusion, on postoperative days 1 and 3. Further similarities between the two studies include comparable baseline SRS scores, and the return to baseline SRS by both IPLA and Control groups at day 30 postoperation. An increased

frequency of assessment prior to day 30 is required to determine the earliest time point at which recovery scores achieve baseline, or whether IPLA hastens the return to baseline scores.

Interestingly, in the current study enhanced recovery was again identified in the IPLA group at day 7 postoperation, during the intermediate to late phase of recovery. This finding is in contrast to the study of Kahokehr and colleagues, where the postoperative recovery scores were similar between IPLA and Control groups at day 7 postoperation. The explanation for the difference between the studies is not known, however it could be postulated that the delayed effect of IP ropivacaine on recovery is dose dependent such that the higher total IP instillation dose of 200mg in the current study in comparison with 75mg, or the higher IP infusion rate of 20mg/hr compared with 8mg/hour was required for an effect to be produced. Alternatively, it may reflect the differences between the two study populations, where in the current study 60% of participants underwent laparoscopically-assisted colectomy in contrast with 3% of study participants in the study by Kahokehr and colleagues.

When the subset of participants who underwent colectomy by the laparoscopic approach were considered separately, it remained true that intraoperative instillation and postoperative infusion of IPLA resulted in enhanced recovery at day 7, during the intermediate to late phase of recovery. Enhanced recovery was additionally identified at day 30 postoperation in the IPLA group, although the relevance of this difference when SRS scores approximate baseline is unclear. IPLA did not, however, enhance functional recovery during the infusion period. It is not known whether this subset analysis is simply not powered to detect the effect of IPLA on recovery during the infusion period or whether there is a difference between the open and laparoscopic subgroups in the effect of IPLA. It is highly possible that the subset analysis is not powered to detect the effect of IPLA on recovery during the infusion peiord. Laparoscopic colectomy is well known to have an improved postoperative recovery compared with open colectomy, based on studies of of recovery that were conducted prior

to development of the SRS tool. These studies demonstrate laparoscopic colectomy results in a reduced postoperative pain, duration of ileus, and length of hospital stay [2 8] compared with open colectomy. It is therefore likely that early SRS scores would be ameliorated by the laparoscopic approach, resulting in attenuation of the effect of IPLA on SRS. Therefore, in laparoscopic colectomy a greater number of participants may be required for the study to be powered to show an effect of IPLA on recovery during the infusion period,

In the current study, IPLA as an intraoperative bolus dose followed by postoperative infusion also led to a significant improvement in postoperative pain as determined by VAS scores. This was expected on the basis of the previous similar finding in an RCT that investigated the effect of a bolus dose of IPLA on postoperative analgesia in laparoscopic colectomy[47], and the level 1 evidence for the analgesic role for IPLA as an intraoperative bolus dose in a broad range of other abdominal surgeries, including laparoscopic and open gynaecological procedures[41 44 45], and laparoscopic gastric procedures[42 143], and. In both the current study and the study of Kahokehr and colleagues[1], the analgesic effect of IPLA was present not only for the duration of infusion, but also at day 7, implying that there is an imprinting effect of IPLA on subsequent nociception. Improved pain at day 7 did not occur in the subset of laparoscopic colectomy. The findings in the current study of improved pain scores that persist beyond the cessation of IPLA infusion to day 7, and of improved recovery scores during the intermediate and late phases of functional recovery are consistent with the concept that IPLA acts locally [144-146] to dampen the vagally mediated neuro-immuno-humoral (NIH) axis surgical stress response to visceral peritoneum injury [48].

IPLA appeared to improve the recovery of bowel function. In the current study, participants that received IPLA passed flatus earlier and demonstrated a weak statistical trend toward earlier bowel movement when compared with Control participants. This finding did not remain true in the subset of

laparoscopically-assisted colectomies. An earlier passage of flatus was previously noted following augmentation of epidural anaesthesia with IPLA following open colectomy in adults[1]. Earlier passage of flatus was also noted when IP ropivacaine was administered to children during laparoscopic herniorrhaphy[147] The mechanism by which IPLA may act to improve recovery of gut function is unknown, but could be either through modulation of the NIH-axis and/or the result of the trend to decreased opioid consumption.

4.3 Study Limitations

In this study assessing the effect of IPLA on functional postoperative recovery following colectomy the sample size required to detect a change in SRS was determined and an improvement in SRS was identified. This study was not powered to show a difference in the remaining domains of postoperative recovery, including reduction in incidence and duration of ileus and time to readiness for discharge. Nor was it powered to demonstrate a statistical difference in reduction in opioid consumption as previously described in level 1 evidence to accompany an improvement in postoperative pain [1 42 43 47]. Although not powered to this outcome, prior studies have demonstrated this effect with as few as 30 participants per study arm. Perhaps in this study the ability to identify only a trend towards a decreased opioid use in the IPLA group is due to a clinical ceiling effect for opioid use, such that at the higher levels of opioid use the responsible clinican was likely to commence a ketamine infusion rather than continue to increase the dose of administered opioid. Interestingly, there was a statistically significant increase in the rate of rescue ketamine in the Control, compared with the IPLA group.

Ropivacaine dosing in the current study was determined on the basis of prior studies describing the pharmacokinetic profile, safety and efficacy of ropivacaine at varied doses. While in this study plasma concentrations of ropivacaine were not measured, participants were screened for signs and

symptoms of ropivacaine toxicity throughout the infusion period. There was no difference in the rate of symptom reporting between the Control and IPLA groups, however one potentially toxic event was identified. This was suspected to be related to underlying undiagnosed liver disease, known to reduce the capacity for ropivacaine metabolism.

This study was limited by availability of potential participants, although it had a standard recruitment rate. Two additional recruitment sites were opened in order to facilitate participant recruitment and completion of the laparoscopic arm of the study was achieved.

4.1 Study Strengths

This study was small, but was able to determine a significant difference in SRS between the intervention and control groups. Therefore, the magnitude of the effect of the intervention was large. The research question was able to be answered in a shorter amount of time and over fewer centres with limited cost to the institutions involved.

The study design was modelled on the research of Kahokehr and colleagues[1], and wherever possible used validated and standardized assessment methods, permitting the study to be replicated by different clinical groups, and over time, with the production of comparable findings. Clear documentation is provided regarding the content and application of the survey instruments so that other researchers can assess the validity of the findings.

This study was inclusive of all patients undergoing elective colectomy at each study centre, and therefore an accurate representation of the South Australian population. The findings can be generalized to the Australian population.

This study is a prospective double-blind randomised controlled trial and therefore can establish causation, and is not subject to allocation bias, selection bias, patient or observer bias. Recruitment bias remains present in all RCTs. The impact of nonresponse bias to the patient reported outcome

SRS is not known. The randomisation was stratified by surgical approach, allowing subgroup analysis of participants undergoing laparoscopically-assisted colectomy. This study was designed to determine the benefits and risks of the intervention as it would occur in routine clinical practice. This provides information on the comparative effectiveness of the intervention when employed by clinicians in the hospital, where patients have complex medical conditions and institutions have systematic differences in the capacity to complete an intervention. The result can therefore inform clinical practice.

4.1 Conclusions and Future Directions for Research

This double-blind randomised controlled trial (RCT) has demonstrated a benefit of intraperitoneal local anaesthetic (IPLA) instillation and postoperative infusion to functional postoperative recovery following colectomy, most apparent during the late phase of recovery when the patient has been discharged to home. IPLA also resulted in improved pain scores during the intermediate recovery phase, and earlier return of postoperative bowel function. IPLA may therefore may be regarded as a successful standalone treatment with an impact in the late phase of recovery, likely through modulation of the NIH-axis response to surgery, or in other words, a dampening of the surgical stress response. IPLA can therefore be recommended for inclusion into the ERAS polypharmacy approach to postoperative pain management following laparoscopic colectomy. IPLA has the potential to reduce the patient hospital length of stay and cost to the health system. We propose that while we did not show improvement in discharge parameters or postoperative complications, these may be demonstrated in a study with more participants.

The potential benefit of IPLA goes well beyond good postoperative analgesia and improved postoperative functional recovery. In recent research the magnitude of the peritoneal cytokine response has been linked to the degree of postoperative metabolic derangement, presence and

duration of ileus, formation of adhesions and oncological outcomes. The potential benefit of IPLA to impact upon these factors should be evaluated in future research.

5. Appendix

5.1 Participant Information Sheet and Consent Form

Dear

You are invited to be a participant in a study about infusion of local anaesthetic into the abdomen and how well that reduces pain and improves recovery after bowel surgery

This study is available to patients having bowel surgery at Calvary North Adelaide Hospital, St Andrew's Hospital and The Royal Adelaide Hospital. Participants will receive a standard post-operative pain relief regimen and in addition will also have a "Painbuster" that delivers local anaesthetic (or saline) into the abdomen to the operation site for 48 hours.

Participants are required to complete a diary that contains questionnaires about pain levels and recovery markers at different times after their surgery. Participants are also asked to record details such as first drink, food and flatus. Questionnaires are asked on day 1, 2, 3, 7, 30 and 45 after surgery. The Clinical Coordinator will remind participants on the day to complete the questionnaire.

Participation is voluntary. You may choose to discontinue participation at any time during the trial. Your decision not to take part in this trial, or to stop participating in this trial will not affect your current or future medical care or your relationship with employees of Calvary North Adelaide Hospital, St Andrew's Hospital or the Royal Adelaide Hospital.

If you have any questions please contact the Study Coordinator Dr Jaime Duffield on 0418329970.

Sincerely

Dr Jaime Duffield

Participant Information Sheet/Consent Form

Interventional Study – *Adult providing own consent*

Title	The Effect of Intraperitoneal Local Anaesthetic on Functional Recovery Following Bowel Resection: A Prospective Randomised Blinded Trial.
Short Title	Intraperitoneal Local Anaesthetic (IPLA) Study
Protocol Number	**150219**
Coordinating Principal Investigator	Dr Jaime Duffield BSc(Hons) BMBS PhD
Principal Investigators	Dr Michelle Thomas MBBS FRACS PhD Dr Mark Lewis MBBS FRCS
Locations	Royal Adelaide Hospital, St Andrew's Hospital and Calvary North Adelaide Hospital

Part 1 What does my participation involve?

1. Introduction

You are invited to be a participant in a study about infusion of local anaesthetic into the abdomen and how well that reduces pain and improves recovery after bowel surgery

This study is available to patients having bowel surgery at Calvary North Adelaide Hospital, St Andrew's Hospital and The Royal Adelaide Hospital. Participants will receive a standard post-operative pain relief regimen and in addition will also have a "Painbuster" that delivers local anaesthetic (or saline) into the abdomen to the operation site for 48 hours.

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This Participant Information Sheet/Consent Form tells you more about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

2. What is the purpose of this research?

This study aims to assess if, in addition to our suite of standard pain medications, infusion of a long-acting local anaesthetic called "Ropivacaine" into the abdomen after surgery can provide further pain relief, and further improve postoperative recovery. The theory is that local anaesthetic into the abdomen will treat an additional type of pain, "visceral pain", which does not respond as well as the "somatic pain" from your skin incisions does to standard pain medications.

Medication, drugs and devices have to be approved for use by the Therapeutic Goods Administration (TGA). A ropivacaine infusion into a wound using a painbuster catheter device is approved in Australia to treat post-operative pain. We will assess how this use improves your recovery following bowel surgery.

If Ropivacaine infusion into the abdomen provides a significant improvement to postoperative pain and recovery then we will add this treatment to our standardised protocol for the management of people having bowel surgery.

This research has been initiated by the Colorectal Surgical Unit and the study doctor, Dr Jaime Duffield.

3. What does participation in this research involve?

You will need to sign a consent form prior to any study assessments being performed.

As part of your normal work-up for bowel surgery you will be asked a series of health related questions and have blood tests. These will be used to determine if you are eligible to participate in the research project.

If eligible, you will be participating in a double-blind randomised placebo-controlled research project.

- Double-blind means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.

- A placebo is a medication with no active ingredients or a procedure without any medical benefit. It looks like the real thing but is not. In this study the placebo will be saline solution, the same fluid that is used in a drip.
- Sometimes to find out if a treatment for a condition has any effect we compare the treatment to a placebo. We put people into groups and give one group the treatment and the other group the placebo, and compare the results between groups. To try to make sure the groups are equal, each participant is put into a group by chance (random), and we call the study randomised.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You will receive the standard care for a person having bowel surgery at the Royal Adelaide Hospital, St Andrew's Hospital or Calvary North Adelaide Hospital.

As part of your standard care, after your operation you will be provided regular panadol and a Patient Controlled Analgesia (PCA) pump connected to your drip line that will allow you to self-administer a strong pain medication called fentanyl or morphine. The anaesthetists will manage your use of the PCA, and when you do not need it anymore they will remove it and you will be able to ask your nurse for extra pain relief medication as you need it.

In addition to that standard care, during your operation and while you are asleep your surgeon will place a thin catheter, like a drip line, into the abdomen and fix it to your skin with a dressing so it cannot be accidentally removed. It will be connected to an infusion device called a "painbuster", about the size of a tennis ball, which you will carry with you for 48 hrs using a small shoulder bag. This device will contain the infusion fluid. It will be removed after 48hrs and will feel the similar to the removal of your drip line.

You will be provided with a diary that will prompt you to provide a score reflecting your level of pain and fatigue at certain times after your operation has finished. You will be required to record details such as when you first drank, ate, and when you first passed wind (flatus) and stool. The principal investigator will visit you while in hospital to ensure you are happy with your progress.

As part of standard care you will be discharged from hospital when:

1. you have passed wind or a bowel motion
2. you are able to tolerate oral diet without nausea or vomiting
3. you are able to mobilise safely
4. your pain medication requirement is for oral tablets only.

Following discharge, you will have follow up appointment with your Colorectal Surgeon as per normal protocol. In addition, as part of this research project, you will be contacted by the principal investigator to determine your satisfaction with the research project and to provide a score reflecting your level of pain, and fatigue at day 7, day 30 and day 45 after operation.

4. What do I have to do?

As part of this research project you will be required to complete your research project diary while you are in hospital and after you have gone home to provide scores that reflect your level of pain and fatigue at day 7, day 30 and day 45 after operation

5. Other relevant information about the research project

50 people having open bowel surgery and 50 people having laparoscopic bowel surgery will be able to participate in this research project. Half of those participants will receive an abdominal infusion of Ropivacaine and half of saline solution.

This research project is limited to people receiving care at The Royal Adelaide Hospital, St Andrew's Hospital, or Calvary North Adelaide Hospital.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. You do not have to provide any explanation for your decision.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with either The Royal Adelaide Hospital or St Andrew's Hospital.

7. What are the alternatives to participation?

You do not have to take part in this research project. The alternative is standard management for your medical condition.

8. What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research.

9. What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Side Effects of Ropivacaine				
Side Effects	**Symptoms**	**How often is it likely to occur?**	**How severe might it be?**	**How long might it last?** (If symptoms related to the drug and the drug is stopped)
Nervous system	Decreased sensation of other body parts, fever or chills, headache, dizziness	> 1%	Mild	2-4 hours
	No sensation of other body parts	≤ 1%	Mild	
Heart	Low blood pressure	> 10 %	Moderate	2-4 hours
	Slow heart rate, high blood pressure and fast heart rate	> 1 %	Moderate	
Gastrointestinal	Nausea	> 10 %	Mild	2-4 hours
	Vomiting	> 1 %	Mild	
Other	Urinary retention	> 1 %	Moderate	2-4 hours
	Anxiety	≤ 1%	Mild	
Toxicity	Tingling of numbness of mouth and tongue	Unlikely as we will use a dose shown to be below the levels required to develop toxicity	These symptoms appear in order and therefore there are reversible minor signs of toxicity present before serious problems occur. If you report these symptoms your treatment will be discontinued.	15-25min
	Inability to properly form words while speaking			
	Light-headedness			
	Visual and hearing disturbances			
	Muscle twitching			
	ECG changes			
	Cardiac arrest			
Allergy	Anaphylaxis	Rare	Severe, may result	Variable

	Cardiac arrest		in death	

Severe side effects reported for Ropivacaine are similar to those observed with similar other local anaesthetics. These may result from overdosage, accidental intravenous injection, or delayed absorption or metabolism of the drug. They should not be confused with the normal effects of the drug. The doses of Ropivacaine proposed for use inside the abdomen in this study have been used previously, but have not been studied before.

The use of an infusion device is associated with a low risk of catheter associated infection. If this happens, it can be easily treated. Your surgical team will be monitoring you for signs of infection as part of your normal management.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

10. What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11. Can I have other treatments during this research project?

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

12. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to collect

your research project diary and discontinue collection of other data relevant to you in the study.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the research team up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13. Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The drug/treatment/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing

14. What happens when the research project ends?

If Ropivacaine infusion into the abdomen provides a significant improvement to postoperative pain and recovery then we will add this treatment to our standardised protocol for the management of people having bowel surgery.

On request, participants will be forwarded a summary of results at the completion of this study. This will be towards the end of 2016.

Part 2 How is the research project being conducted?

15. What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. This information will be stored in a hard copy and electronic file in the Research Office of the Colorectal Surgical Unit, Royal Adelaide Hospital which is subject to the normal confidentiality restraints of personal information within the hospital environment, such as a coded lock on the door and password protected electronic devices. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to

the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the institution relevant to this Participant Information Sheet, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project will be recorded in your health records.

In accordance with relevant Australian and/or South Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

16. Complaints and compensation

If you have a concern or complaint regarding your treatment by a member of staff this should be directed to their manager or to the hospital patient advocate officer, contactable through the switchboard.

If you have a concern or complaint directly related to the research project this can be directed to a member of the study team or to the hospital patient advocate officer, contactable through the switchboard.

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In the event of loss or injury, the parties involved in this research project have agreed to manage your claim in the same manner as any claim arising from treatment during admission under the Consultant Colorectal Surgeon.

17. Who is organising and funding the research?

This research project is being conducted by Dr Jaime Duffield, Colorectal Surgical Unit, Royal Adelaide Hospital.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

You will not benefit financially from your involvement in this research project. In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

18. Who has reviewed and approved the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HRECs of The Royal Adelaide Hospital, St Andrew's Hospital and Calvary North Adelaide Hospital.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19. Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor, Dr Jaime Duffield on mobile 0418329970, or your Colorectal Surgeon.

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Patient Services Advocate via RAH switchboard: 8222 4000 Or
HREC Executive Officer **Ms Heather O'Dea**
Level 3, Hanson Institute, RAH
Phone: (08) 822**2 4139**
Fax: (08) 822**2 3035**
Email: heather.o'dea@health.sa.gov.au

Consent Form – *Adult providing own consent*

Title	The Effect of Intraperitoneal Local Anaesthetic on Functional Recovery Following Bowel Resection: A Prospective Randomised Blinded Trial.
Short Title	Intraperitoneal Local Anaesthetic (IPLA) Study
Protocol Number	**150219**
Coordinating Principal Investigator	Dr Jaime Duffield BSc(Hons) BMBS PhD
Locations	Royal Adelaide Hospital & St Andrew's Hospital

Declaration by Participant

I am 18 years of age or older.

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to the Royal Adelaide Hospital or St Andrew's Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to discuss this information with a family member or friend.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I may not benefit from taking part in this study.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/

Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

5.2 Naropin Product Information PAIN.000-114-897.7.0

NAROPIN Product Information
PAIN.000-114-897.7.0

NAROPIN®

Ropivacaine Hydrochloride

PRODUCT INFORMATION

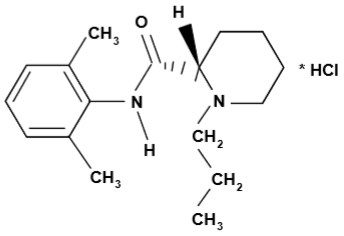
(Injection solutions for the production of local or regional anaesthesia)

NOT FOR INTRAVENOUS ADMINISTRATION UNDER ANY CIRCUMSTANCES

NAME OF THE MEDICINE

The active ingredient in NAROPIN® is ropivacaine hydrochloride. The CAS number for the free base is 84057-95-4. The chemical formula of ropivacaine hydrochloride is $C_{17}H_{26}N_2O.HCl.H_2O$.

The chemical structure of ropivacaine hydrochloride is:



DESCRIPTION

The chemical name for ropivacaine hydrochloride is (S)-(-)-propyl-piperidine-2-carboxylic acid (2,6-dimethyl-phenyl)-amide hydrochloride monohydrate. It is a white crystalline powder and has a water solubility of about 50 mg/mL. Ropivacaine hydrochloride was developed as the pure S-(-)-isomer and has an enantiomeric purity of > 99%. It has a pKa of 8.1 (at 25 °C) and a molecular weight of 328.89. The pH of a saturated solution of ropivacaine hydrochloride is 4.5 and that of a 1% (w/v) aqueous solution is 5.0.

NAROPIN solution for injection is a sterile, isotonic, isobaric, aqueous solution of ropivacaine HCl in Water for Injections BP. The pH of the solution is adjusted with sodium hydroxide or hydrochloric acid to remain between 4.0 - 6.0 during the approved shelf-life. The nominal osmolality of NAROPIN 0.2% (2 mg/mL) is 288 mosmol/kg. The solution is preservative free.

The presentations of NAROPIN injection solutions are intended for single use only. Any solution remaining from an opened container should be discarded.

PHARMACOLOGY

Ropivacaine has both anaesthetic and analgesic effects. At higher doses it produces surgical anaesthesia with motor block, while at lower doses it produces a sensory block including analgesia with little motor block.

The duration and intensity of ropivacaine sensory block is not improved by the addition of adrenaline.

Ropivacaine, like other local anaesthetics, causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. It is the first long acting amide local anaesthetic developed as a pure enantiomer. There is no evidence of *in vivo* racemisation of ropivacaine.

Pharmacodynamics and tolerability

The local anaesthetic effect of ropivacaine and its R-(+) enantiomer was evaluated for sciatic block, spinal anaesthesia and infiltration anaesthesia over a wide concentration range (0.25 - 1.0%) in a number of animal species and a concentration-(dose-) response relationship was ascertained. These studies supported the selection of the enantiomerically pure drug ropivacaine and are consistent with the observations with other local anaesthetics that the S-(-) form is less toxic and/or has a longer duration of action than the R-(+) form.

In vitro testing of ropivacaine conduction anaesthesia indicate that ropivacaine is comparable to, or slightly more potent than, bupivacaine in blocking sensory fibres and is less active in blocking motor fibres.

The anaesthetic effects of ropivacaine were evaluated in peripheral (sciatic nerve and brachial plexus) and central (spinal and epidural) neural blocks, as well as in infiltration and topical anaesthesia in a large number of studies using multiple animal species including mouse, rat, guinea-pig, dog, sheep and Rhesus monkey.

The peripheral neural block studies indicate that a concentration of ropivacaine of 0.5 - 1.0% consistently produces effective sensory and motor block. Neither increasing concentration above 0.75% nor adding adrenaline significantly improved the duration of motor block or anaesthesia with ropivacaine.

For central neural blockade, for all species studied, it appeared that onset times of epidural anaesthesia with ropivacaine and bupivacaine were similar. The concentration required to consistently produce complete motor blockade with epidural anaesthesia appeared to be 0.75 - 1.0% for ropivacaine. Duration of sensory block appeared to be comparable for equal concentrations of ropivacaine and bupivacaine.

Tests of infiltration anaesthesia in guinea-pigs showed that ropivacaine was markedly superior to bupivacaine in producing sustained cutaneous anaesthesia at all concentrations. The duration of anaesthesia produced with the least effective ropivacaine concentration (0.25%) far exceeded that produced by the highest bupivacaine concentration (0.75%).

For analgesia, the potency of ropivacaine is similar to that of bupivacaine. For motor block, the potency was found to be around 80% of bupivacaine.

Ropivacaine and bupivacaine are equipotent in producing seizures in rats and dogs. In both pregnant and non-pregnant sheep, ropivacaine was less toxic than bupivacaine.

Comparisons with the short acting local anaesthetic lignocaine shows that the doses needed to produce seizures are 2 (in sheep) to 4 (in rats and dogs) times the dose of ropivacaine. In studies in sheep, ropivacaine appears to have less central nervous system and cardiovascular toxicity than bupivacaine, and pregnancy does not appear to enhance sensitivity in either the central nervous system or in cardiac membranes as has been reported in some studies with bupivacaine.

In vitro heart studies indicate that the effects of ropivacaine on conduction and contractility are less compared to bupivacaine. The risk of ventricular tachycardia is less with ropivacaine than bupivacaine. Atrial and ventricular pacing were more successful during exposure to high concentrations of ropivacaine compared to bupivacaine. The *in vitro* electrophysiological studies are consistent with the findings in the *in vitro* heart preparation.

Cardiovascular effects measured *in vivo* in animal studies showed that ropivacaine is consistently well tolerated and that ropivacaine is less likely than bupivacaine to produce ventricular arrhythmias. Resuscitative measures were highly successful in dogs given large overdoses (9.8 mg/kg given intravenously) of ropivacaine. In most preclinical studies of the cardiovascular effects, comparisons were also made with lignocaine. In general all results were consistent with the observation that a given dose of lignocaine was less toxic than an equivalent dose of ropivacaine or bupivacaine.

In man, ropivacaine is less toxic regarding the CNS and cardiovascular systems than bupivacaine. In two tolerability studies in volunteers given IV infusions, CNS symptoms appeared at higher doses and higher free plasma concentrations of ropivacaine compared to bupivacaine. The ropivacaine dose-response and concentration-response curves for CNS symptoms, e.g. muscular twitching, dysarthria, were consistently shifted to the right compared with those of bupivacaine. A threshold for CNS toxicity was apparent at a free plasma concentration of 0.34 mg/L ropivacaine and 0.13 mg/L bupivacaine. Ropivacaine caused a smaller increase in the QRS width and less pronounced reduction in diastolic and systolic function of the left ventricle as compared to bupivacaine.

2,6-pipecoloxylidide (PPX) is an active metabolite. The threshold for systemic CNS-toxic unbound plasma concentrations of PPX in rats is about twelve times higher than that of unbound ropivacaine.

Factors which may increase the relative systemic toxicity of local anaesthetics are acidosis and severe hepatic dysfunction.

Ropivacaine, like bupivacaine and other local anaesthetics, produces vasoconstriction at lower concentrations and vasodilation at higher concentrations. These findings appear to be consistent both *in vivo* and *in vitro*.

Pharmacodynamic interactions

In preclinical studies in rats, ropivacaine interacts with agents used in conjunction with regional anaesthesia, such as benzodiazepines, thiopental, enflurane, pancuronium, suxamethonium and fentanyl, in a manner similar to that produced by the commonly used local anaesthetics bupivacaine and lignocaine. In rats, pretreatment with ropivacaine potentiated the sedative effect of morphine compared to placebo.

Pharmacodynamic drug interactions of local anaesthetics probably depend more on the physiological effects of the block, such as hypotension and bradycardia, than on circulating blood levels of the local anaesthetic.

Pharmacokinetics

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Ropivacaine has linear pharmacokinetics and the maximum plasma concentration is proportional to the dose.

Ropivacaine shows complete and biphasic absorption from the epidural space with half-lives of the two phases in the order of 14 minutes and 4 hours. The slow absorption is the rate limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine shows a biphasic absorption from the caudal epidural space also in children.

The pharmacokinetic profile of ropivacaine in adults following experimental IV administration is summarised below:

Plasma clearance	440 mL/min
Unbound plasma clearance	8 L/min
Renal clearance	1 mL/min
Volume of distribution at steady-state	47 L
Unbound volume of distribution at steady-state	819 L
Terminal half-life	1.8 h
Unbound fraction	0.06
Hepatic extraction ratio	0.4
Major metabolite	3-OH-ropivacaine

Ropivacaine is mainly bound to α_1-acid glycoprotein in plasma with an unbound pharmacologically active fraction of about 6%. An increase in total plasma

concentrations during continuous postoperative epidural infusion and interscalene infusion has been observed. This increase is related to a postoperative increase of α_1-acid glycoprotein. Variations in unbound concentration of ropivacaine have been much less than in total plasma concentration.

Ropivacaine is extensively metabolised, predominantly by aromatic hydroxylation. In total, 86% of the dose is excreted in the urine after intravenous administration, of which only about 1% is unchanged drug. Approximately 9% is excreted in faeces.

Both the dealkylation (N-depropylated or PPX) and the hydroxylation pathways in the metabolism of ropivacaine are detoxification reactions. PPX is considered to have approximately one twelfth of the pharmacological activity of ropivacaine. The hydroxylated metabolites of ropivacaine have some local anaesthetic activity (ropivacaine > 3-hydroxy-ropivacaine >> 4-hydroxy-ropivacaine). The hydroxylated metabolites are rapidly conjugated in human plasma and are very unlikely to have any pharmacological or toxicological activities.

The major metabolite is 3-hydroxy-ropivacaine. This metabolite accounts for about 37% of urinary excretion, mainly as a glucuronide conjugate. The only metabolite which reaches detectable concentrations in plasma is 3-hydroxy-ropivacaine (conjugated and unconjugated). Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite and the 4-hydroxy-dealkylated metabolite accounts for 1 - 3% of a given dose.

The NADPH-dependent metabolism of ropivacaine to 3-hydroxy-ropivacaine is catalysed by CYP1A2. The formation of minor metabolites *in vivo* is catalysed by CYP3A4. The apparent Km (affinity constant) for 3-hydroxy-ropivacaine is 16 µM and about 400 µM for the other metabolites. Of the two members in the CYP1A family, CYP1A1 is expressed only after exposure to inducers, while CYP1A2 accounts for about 10% of total P450 in the liver (see Metabolic interactions).

A similar pattern of metabolites has been found in children above one year.

Impaired renal function has little or no influence on ropivacaine pharmacokinetics. The renal clearance of PPX is significantly correlated with creatinine clearance. A lack of correlation between total exposure, expressed as AUC, with creatinine clearance indicates that the total clearance of PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to PPX resulting from a low non renal clearance. The potential for toxicity in these patients is dependent on the total dose, dose route and duration of exposure to ropivacaine.

Paediatrics

The pharmacokinetics of ropivacaine was characterized in a pooled population PK analysis on data in 192 children between 0 and 12 years from six studies (3 on caudals, 2 on epidural infusions, and 1 on ilioinguinal block). Unbound ropivacaine and PPX clearance and ropivacaine unbound volume of distribution initially depend on both body weight and age up to three years of age, after which they depend largely on body weight. The maturation of unbound ropivacaine clearance

appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound ropivacaine volume of distribution by the age of 2 years. The PPX unbound volume of distribution only depends on body weight.

Unbound ropivacaine clearance increases from 2.4 and 3.6 L/h/kg in the newborn and the 1- month neonate to about 8-16 L/h/kg for ages above 6 months, values within the range of those in adults. Total ropivacaine clearance values per kg body weight increase from about 0.10 and 0.15 L/h/kg in the newborn and the 1-month neonate to about 0.3 - 0.6 L/h/kg beyond the age of 6 months. Unbound ropivacaine volume of distribution per kg body weight increases from 22 and 26 L/kg in the newborn and the 1-month neonate to 42 - 66 L/kg above 6 months. Total ropivacaine volume of distribution per kg body weight increases from 0.9 and 1.0 L/kg for the newborn and the 1-month neonate to 1.7 - 2.6 L/kg beyond the age of 6 months. The terminal half-life of ropivacaine is longer, 6 to 5 h in the newborn and the 1-month neonate compared to about 3 h in older children. The terminal half-life of PPX is also longer, from 43 and 26 h in the newborn and the 1-month old neonate to about 15 h in older children.

At 6 months, the breakpoint for change in the recommended dose rate for continuous epidural infusion, unbound ropivacaine clearance has reached 34% and unbound PPX 71% of its mature value. The systemic exposure is higher in neonates and also somewhat higher in infants between 1 to 6 months compared to older children which is related to the immaturity of their liver function. However, this is partly compensated for by the recommended 50% lower dose rate for continuous infusion in infants below 6 months.

Simulations on the sum of unbound plasma concentrations of ropivacaine and PPX, based on the PK parameters and their variance in the population analysis, indicate that for a single caudal block the recommended dose must be increased by a factor of 2.7 in the youngest group and a factor of 7.4 in the 1 to 10 year group in order for the upper prediction 90% confidence interval limit to touch the threshold for adult systemic toxicity. Corresponding factors for the continuous epidural infusion are 1.8 and 3.8 respectively.

When comparing descriptive data in a trial of caudal/epidural infusions in 10 full term neonates aged 0-30 days, to that in 18 older patients aged 31-180 days, total and unbound ropivacaine was higher and showed higher inter-individual variability, unbound apparent clearance lower and ropivacaine binding to plasma proteins (AAG) was lower. There was a greater relative excretion of ropivacaine in urine. Plasma concentrations of total and unbound PPX were similar but PPX had a longer half-life. The sum of unbound concentrations of ropivacaine and one twelfth of PPX was higher in neonates 0-7 days. While the highest level reached was 0.24 mg/L, this may have been still rising when observations ceased at 72 h (only 4 observations). The systemic CNS toxicity threshold in adults is 0.34 mg/L in a mature nervous system (see Pharmacodynamics and tolerability). It is not known how immaturity of the CNS affects toxic thresholds.

Foetuses exposed to ropivacaine during labour or Caesarean section can be regarded, after they have been born, as neonates with a peak plasma concentration at the time of delivery. The maximum unbound plasma ropivacaine

concentrations in the newborn as reflected in the umbilical vein at delivery, 0.03 to 0.11 mg/L, are in the same range as those seen after single caudal block in neonates and support the documentation of ropivacaine in neonates.

Neonatal exposure based on umbilical venous plasma concentrations at delivery after epidural block for Caesarean section with ropivacaine 115 to 150 mg or continuous lumbar epidural infusion with 25 mg/h in labour.

Delivery		n	Mean	SD	Median	Min	Max
Caesarean section	C_{max} (mg/L)	71	0.33	0.16	0.30	0.11	1.12
	$C_{u,\,max}$ (mg/L)	69	0.07	0.02	0.07	0.03	0.11
	f_u (%)	69	21.6	6.6	22.2	6.1	34.4
Labour	C_{max} (mg/L)	10	0.32	0.13	0.34	0.13	0.52
	$C_{u,\,max}$ (mg/L)	10	0.05	0.01	0.04	0.03	0.07
	f_u (%)	10	16.8	8.6	12.5	8.5	30.2

Pharmacokinetics during pregnancy at term

In pregnancy at term, ropivacaine clearance is somewhat lower and its unbound clearance about half of that seen after epidural administration to non-pregnant patients. Accordingly, total C_{max} and unbound C_{max} are higher in pregnancy. The unbound plasma concentrations in the umbilical vein at delivery were similar to those in the mother and showed a fairly rapid equilibrium. There was no obvious correlation between neonatal neurologic and adaptive capacity scores and unbound or total plasma concentrations in the newborns.

Epidural Injection

Two parallel groups of 10 patients each, scheduled for epidural analgesia to relieve pain during labour, received ropivacaine or bupivacaine as a 50 mg bolus followed on request by a 25 mg top-up dose.

The unbound concentration of ropivacaine was higher than that of bupivacaine at 20 min, 0.04 (0.013) mg/L and 0.02 (0.008) mg/L as well as at 4 hours after the initial dose, 0.03 (0.006) mg/L and 0.02 (0.013) mg/L. The mean unbound fraction of ropivacaine was higher, 0.07, than that of bupivacaine, 0.04.

Epidural Infusion

Patients scheduled for epidural analgesia as pain relief during labour received a continuous lumbar epidural infusion of ropivacaine 12.5 mg/h, 25 mg/h or bupivacaine 25 mg/h after an initial dose of 12.5 mg (ropivacaine) or 25 mg (ropivacaine or bupivacaine). Treatment with ropivacaine 12.5 mg/h was terminated after 6 patients had been withdrawn due to insufficient analgesia. The results in the two groups of 10 patients each given 25 mg/h of ropivacaine or

bupivacaine (2.5 mg/mL) are described below. The rate of infusion (dose) was not changed during the course of the study.

The median duration of the infusion was 6.6 hours with ropivacaine and 7.7 hours with bupivacaine, corresponding to total mean doses of 179 and 227 mg.

The maternal unbound fraction was higher after ropivacaine than after bupivacaine. The unbound plasma clearance of ropivacaine, 3.35 (1.36) L/min, was about half of that of bupivacaine, 6.40 (2.47 L/min). The mean (SD) umbilical venous unbound fraction was 0.17 (0.09) with ropivacaine and 0.12 (0.05) with bupivacaine. The unbound UV/MV ratios did not seem to increase with the duration of the infusion, indicating rapid equilibration.

Umbilical arterial (UA) and venous (UV) unbound concentrations after continuous lumbar epidural infusion of ropivacaine and bupivacaine 25 mg/h in labour are presented in the following table.

Umbilical arterial (UA) and venous (UV) unbound concentrations after continuous lumbar epidural infusion of ropivacaine and bupivacaine 25 mg/h in labour.

	UA Free (mg/L)
Ropivacaine	
Actual total dose given of ropivacaine HCl 145 - 200 mg	0.027 – 0.058 (n = 4)
Median	**0.036**
Bupivacaine	
Actual total dose given of bupivacaine HCl 93.5 - 227.4 mg	0.014 – 0.021 (n = 2)
Median	**0.017**
	UV Free (mg/L)
Ropivacaine	
Actual total dose given of ropivacaine HCl 99.2 - 255.4 mg	0.027 – 0.067 (n = 10)
Median	**0.042**
Bupivacaine	
Actual total dose given of bupivacaine HCl 93.5 - 365.3 mg	0.011 - 0.035 (n = 9)
Median	**0.025**

CLINICAL TRIALS

Adults

Two open label, randomized uncontrolled clinical studies were performed to document the efficacy and safety of NAROPIN 2 mg/mL in continuous peripheral nerve block for post-operative management up to 48 hours. In total 163 patients were studied, 136 received femoral block and 27 interscalene block. Continuous peripheral nerve blocks with NAROPIN provided effective post operative pain relief in both studies. Patient satisfaction was reported to be high.

Four open label, randomized studies were performed to investigate the efficacy and safety of NAROPIN 0.5% (5 mg/mL) and other strengths for intrathecal administration in surgical anaesthesia. A total 224 patients were studied, of which 217 patients were valid for safety and 212 for efficacy. In two studies, patients underwent minor orthopaedic, gynaecological or urological surgery suited for spinal anaesthesia. In the other two studies, patients underwent a unilateral hip replacement. NAROPIN 15 to 20 mg administered intrathecally was effective and the anaesthetic quality was rated high by surgeons, anaesthetists and patients. The incidence and severity of adverse events reported were not related to dose.

Paediatrics

A total of 5 studies, involving 246 patients aged 0-12 years, were performed to evaluate the use of NAROPIN 2 mg/mL (0.2%) for caudal block (3 studies) and continuous epidural infusion (2 studies). In the studies on caudal block, the given volumes of the ropivacaine solutions were 1 mL/kg. In one of these studies in paediatric patients between 4 and 12 years of age, three different dosages of NAROPIN (1, 2 and 3 mg/kg, 0.1%, 0.2% and 0.3%) were compared. Adequate efficacy with minimal motorblock was found for the 2 mg/kg dose. In another study on caudal block in neonates and infants between 0 and 12 months of age, the analgesic efficacy was similar to the efficacy in paediatric patients above one year of age, given the same dose per kilogram (2 mg/kg), when assessed as the proportion of patients with postoperative pain, time to first pain and time to treatment with supplementary analgesics.

In two studies in patients 1 day to 12 years old an epidural bolus was followed by a continuous infusion for up to 72 hours. The epidural bolus volume ranged between 0.5 and 1 mL/kg of ropivacaine 2 mg/mL (0.2%), with lower volumes given for thoracic than for lumbar injections. The infusion rate was 0.2 mg/kg/h in neonates and infants below 6 months of age and 0.4 mg/kg/h of ropivacaine 2 mg/mL (0.2%) in patients above 6 months of age. More than 80% of the patients had no/mild pain, or were asleep, at any time point. There was no difference in pain score between the 0 to 6 months group (ropivacaine 0.2 mg/kg/h infusion) and the 6 to 12 months group (ropivacaine 0.4 mg/kg/h infusion). The median time to supplementary analgesia was 3.3 hours in patients older than 1 year, whereas in younger patients less than 40% had been given supplementary analgesia after 72 hours. Motor block was observed in 32% of the patients above 1 year of age but in none of the infants below 1 year of age. Ropivacaine was well tolerated in all paediatric age groups.

INDICATIONS

Surgical anaesthesia (Adults and children over 12 years of age)

- epidural block for surgery including caesarean section
- intrathecal anaesthesia
- field block (minor nerve block and infiltration)
- major nerve block

Analgesia (Adults and children over 12 years of age)

- continuous epidural infusion or intermittent bolus epidural administration for analgesia in postoperative pain or labour pain
- field block (minor nerve block and infiltration)
- continuous peripheral nerve block infusion or intermittent injections for post operative pain management
- continuous wound infusion for postoperative pain management (adults only)

Analgesia (Children aged 0 - 12 years)

- Caudal epidural block in neonates (> 37 weeks gestation and over 2500 g weight), infants and children up to and including 12 years
- Continuous epidural infusion in infants (> 30 days and over 2500 g weight) and children up to and including 12 years
- Peripheral nerve block in children aged 1 up to and including 12 years

For peri- and postoperative pain management.

There are no safety or efficacy data to support the use of NAROPIN for analgesia for longer than 72 hours. (Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections and for continuous wound infusion support the use for up to 48 hours only).

CONTRAINDICATIONS

1. Allergy or hypersensitivity to amide type local anaesthetics. Detection of suspected hypersensitivity by skin testing is of limited value.
2. Intravenous administration.
3. Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension.

4. Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and/or in the presence of septicaemia.

5. Intravenous regional anaesthesia (Bier's block) as unintentional passage of local anaesthetic into the systemic circulation, despite the use of a tourniquet, may cause systemic toxic reactions.

6. The use of NAROPIN is not recommended for obstetric paracervical block.

7. General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

PRECAUTIONS

1. WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND DRUGS, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS. BECAUSE OF THE POSSIBILITY OF HYPOTENSION AND BRADYCARDIA FOLLOWING MAJOR BLOCKS, AN IV CANNULA SHOULD BE INSERTED BEFORE THE LOCAL ANAESTHETIC IS INJECTED.

2. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE TOXIC EFFECTS.

3. ALTHOUGH INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS FOLLOWING ARTHROSCOPIC AND OTHER SURGICAL PROCEDURES IS AN UNAPPROVED USE, THERE HAVE BEEN POST-MARKETING REPORTS OF CHONDROLYSIS IN PATIENTS RECEIVING SUCH INFUSIONS. THE MAJORITY OF REPORTED CASES OF CHONDROLYSIS HAVE INVOLVED THE SHOULDER JOINT; CASES OF GLENO-HUMERAL CHONDROLYSIS HAVE BEEN DESCRIBED IN PAEDIATRIC AND ADULT PATIENTS FOLLOWING INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS WITH AND WITHOUT ADRENALINE FOR PERIODS OF 48 TO 72 HOURS. THERE IS INSUFFICIENT INFORMATION TO DETERMINE WHETHER SHORTER INFUSION PERIODS ARE NOT ASSOCIATED WITH THESE FINDINGS. THE TIME OF ONSET OF SYMPTOMS, SUCH AS JOINT PAIN, STIFFNESS AND LOSS OF MOTION CAN BE VARIABLE, BUT MAY BEGIN AS EARLY AS THE SECOND MONTH AFTER SURGERY. CURRENTLY, THERE IS NO EFFECTIVE TREATMENT FOR CHONDROLYSIS; PATIENTS WHO EXPERIENCED CHONDROLYSIS HAVE REQUIRED ADDITIONAL DIAGNOSTIC AND THERAPEUTIC PROCEDURES AND SOME REQUIRED ARTHROPLASTY OR SHOULDER

REPLACEMENT. THEREFORE, NAROPIN SHOULD NOT BE USED FOR POST-OPERATIVE INTRA-ARTICULAR CONTINUOUS INFUSION.

4. LOW MOLECULAR WEIGHT HEPARINS AND HEPARINOIDS (Spinal/Epidural Haematomas) – When neuraxial anaesthesia (epidural / spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of drugs affecting haemostasis such as NSAIDs, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

5. The safety and efficacy of NAROPIN depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

6. The lowest dosage that results in efficacious anaesthesia should be used (see DOSAGE AND ADMINISTRATION).

   Elderly, young or debilitated patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction, should be given reduced doses commensurate with their age and physical condition.

   Children aged between 0 and 12 years should be given doses commensurate with their weight and clinical status.

7. Ropivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Ropivacaine has an intermediate to low clearance, which depends on its unbound fraction and intrinsic metabolic clearance. NAROPIN should therefore be used with caution in patients with severe hepatic disease.

8. Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal dysfunction may increase the risk of systemic toxicity (see DOSAGE AND ADMINISTRATION).

9. The possibility of hypotension and bradycardia following epidural and intrathecal blockade should be anticipated and precautions taken, including the prior establishment of an intravenous line and the availability of vasopressor drugs, vagolytic drugs and oxygen.

10. Certain local anaesthetic procedures such as injection in the head and neck region, including retrobulbar, dental and stellate ganglion blocks, may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used. The side effects may be similar to the systemic toxicity seen with unintentional intravascular injections of larger doses.

11. NAROPIN should be used with caution in patients with known drug sensitivities.

12. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.

13. Local anaesthetics should be given with great caution (if at all) to patients with pre existing abnormal neurological pathology, e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal anaesthesia when there are serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

14. Major peripheral nerve blocks may involve the administration of a large volume of local anaesthetic in highly vascularised areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption. This can lead to high plasma concentrations.

15. If NAROPIN is administered simultaneously by two or more different routes, the total dose and hence the risk of systemic toxicity should be considered.

16. Patients treated with class III anti-arrhythmic drugs (e.g. amiodarone) should be under close surveillance. ECG monitoring should also be considered, since cardiac effects may be additive.

17. There have been reports of cardiac arrest during the use of NAROPIN for epidural anaesthesia or peripheral nerve blockade, especially after unintentional accidental intravascular administration in elderly patients and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

18. Neonates need special attention due to immaturity of some organs and functions. This is especially important during continuous epidural infusion. If epidural infusions are to be used in neonates, ropivacaine doses must be individually titrated by a specialist in paediatric

anaesthesia. Regular monitoring for systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO_2) is always required for neonates. Monitoring should be continued after completion of infusion due to decreased rates of elimination of ropivacaine in neonates. Dose recommendations have not been established in premature neonates but organ immaturity would be expected to result in even slower elimination.

19. NAROPIN is possibly porphyrinogenic and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in the case of vulnerable patients.

Genotoxicity

Ropivacaine hydrochloride was negative in the Ames salmonella/mammalian microsome mutagenicity test, human lymphocyte chromosome aberration test, mouse micronucleus test, *E. coli* differential DNA repair test, *E. coli* host-mediated DNA repair test in mice, and the somatic mutation and recombination test in *Drosophila melanogaster* (fruit fly), and weakly mutagenic in the mouse lymphoma test. The clinical use of ropivacaine is unlikely to pose any risk of genotoxicity.

Carcinogenicity

Long term animal assays of carcinogenic potential have not been performed.

Effects on fertility

No adverse effects on fertility and reproductive performance were seen in rats over 2 generations following daily subcutaneous administration of ropivacaine from prior to mating through weaning, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose. Increased pup loss in the first 3 days *post partum* was attributed to reduced maternal care.

Effects on ability to drive and use machines

Depending on the dose, local anaesthetics may have a mild effect on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness. Patients should be warned of this possibility and advised not to drive a motor vehicle or operate machinery if affected.

Use in pregnancy – Category B1

There was no evidence of teratogenicity following daily subcutaneous administration of ropivacaine to rats and rabbits during the period of organogenesis, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose. In rats treated similarly with ropivacaine daily from late gestation to weaning, there were no treatment-related effects on late foetal development, parturition, lactation, neonatal viability, or offspring growth. In rats treated from late gestation to weaning, maternal toxicity was elicited at a lower dose and lower unbound plasma concentration with bupivacaine than with ropivacaine.

There are no clinical studies in pre-term pregnant women on the effects of NAROPIN on the developing foetus. NAROPIN should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The epidural use of NAROPIN in obstetrics is well documented and adverse effects have been reported (see ADVERSE EFFECTS: Foetal, neonatal and infant adverse events).

Intrathecal administration has not been documented for caesarean section.

Use in lactation

Subcutaneous administration of ropivacaine to rats from late gestation to weaning, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose, did not effect late foetal development, parturition, lactation, neonatal viability, or offspring growth. Ropivacaine and/or its metabolites are excreted into milk in rats, but excretion into human milk has not been investigated.

Interactions with other medicines

Local anaesthetics and antiarrhythmic drugs

NAROPIN should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide type local anaesthetics, since the toxic effects are additive. Specific interaction studies with NAROPIN and class III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised (see PRECAUTION 15).

Adrenaline

The duration and intensity of ropivacaine sensory block is not improved by the addition of adrenaline.

Alkaline solutions

The solubility of ropivacaine is limited at pH values above 6.0. This must be taken into consideration if adding an alkaline solution since precipitation might occur at higher pH values.

Cytochrome P450 Interactions (see Pharmacokinetics)

Ropivacaine is metabolised by the enzymes CYP1A2 and CYP3A4. Interactions with inducers of these enzymes are not expected to be clinically relevant, however there is a potential for metabolic interaction when NAROPIN is used in combination with a potent enzyme inhibitor.

CYP1A2 Inhibitors

Fluvoxamine

Oral fluvoxamine treatment caused a 70% decrease in ropivacaine clearance and a 3-fold higher AUC in healthy volunteers. Single administrations of NAROPIN should be used with care in patients who are concomitantly receiving a potent

CYP1A2 inhibitor. Repeated administration or long term infusion should be avoided in such patients.

A theoretical possibility of metabolic drug interactions with potent inhibitors of CYP1A2, such as enoxacin, may exist.

CYP3A4 Inhibitors

Ketoconazole

Co-administration with ketoconazole, a potent inhibitor of CYP3A4, has been shown to cause a marginal (15%) decrease in ropivacaine clearance in healthy volunteers.

Theoretical Interactions

Cimetidine, an inhibitor of CYP2E1, did not inhibit the formation of 3-hydroxy-ropivacaine but inhibited some formation of minor metabolites *in vitro*.

Metabolic Interactions

With the low to intermediate hepatic extraction ratio of ropivacaine (mean 0.4), a fall in the liver blood flow is not expected to have a significant influence on ropivacaine clearance (see PRECAUTION 6).

Clinical relevance of interactions

In the clinical experience with NAROPIN, patients usually received NAROPIN in combination with several other therapies. The safety evaluation of NAROPIN is therefore based upon its use in combination with various concomitant treatments. The review of safety data in these studies show that NAROPIN has a safety profile comparable to other amide local anaesthetics used for regional anaesthesia.

These data did not indicate any specific drug interactions that would require special study for the use of NAROPIN as a single-dose or for treatment for less than 24 hours. Furthermore, drugs metabolised by CYP1A2, e.g. paracetamol, have also been used in combination with NAROPIN in the clinical programme, without clinical evidence of metabolic interactions (see Pharmacokinetics).

ADVERSE EFFECTS

Adverse events reported in association with NAROPIN are similar in character to those observed with other local anaesthetics of the amide type.

Adverse reactions may be due to high plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism, or inadvertent intravascular injection. They should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during epidural and intrathecal anaesthesia and events caused by needle puncture (e.g. spinal haematoma, postdural puncture, headache, meningitis and epidural abscess).

Pronounced acidosis, hyperkalaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see OVERDOSAGE). Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

Very common events (>10%)

Cardiovascular: Hypotension[c]

Gastrointestinal: Nausea

Common events (>1%)

A large number of adverse events have been reported during clinical development, the majority related to the expected effects of the block and to the clinical situation rather than reactions to the drug. Thus hypotension and nausea have been registered in 39% and 25%, respectively, of the patients treated in clinical studies.

The following adverse events are considered to be of clinical importance regardless of causal relationship.

Cardiovascular: Bradycardia[a], hypertension and tachycardia.

Nervous system: Paraesthesia, temperature elevation, rigors (chills), headache[a] and dizziness.

Gastrointestinal: Vomiting[a,d].

Other: Urinary retention[a], back pain, insomnia, chest pain, pain and oliguria.

Uncommon events (≤1%)

Acute systemic toxicity: More serious but less common reactions that reflect acute systemic toxicity[b], include dysarthria, muscular rigidity, muscle twitching, unconsciousness, convulsions, hypoxia, hypercapnia, apnoea, severe hypotension, bradycardia, arrhythmias and cardiac arrest. Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block.

Convulsions, grand mal convulsions and seizures have been observed following unintended intravascular injection of NAROPIN.

Due to the low doses used for intrathecal anaesthesia, the potential for systemic toxic reactions is expected to be low.

Psychiatric: Anxiety

Nervous System: Hypoaesthesia[a]

Vascular: Syncope[a]

Respiratory, thoracic and mediastinal: Dyspnoea[a]

General disorders and administration site conditions: Hypothermia[a]

Rare (≤0.1%)

Cardiac disorders: Cardiac arrest, cardiac arrhythmias

General dis*orders and administration site conditions:* Allergic reactions (anaphylactoid reactions, angioneurotic oedema and urticaria)

a These reactions are more frequent after spinal anaesthesia
b These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption
c Hypotension is less frequent in children (>1%)
d Vomiting is more frequent in children (>10%)

Class related adverse drug reactions

This section includes complications related to anaesthetic technique regardless of the local anaesthetic used.

Neurological complications

Neuropathy and spinal cord dysfunctions (eg, anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome), have been associated with intrathecal and epidural anaesthesia.

Total spinal block

Total spinal block may occur if an epidural dose is inadvertently administered intrathecally, or if a too large intrathecal dose is administered.

Foetal, neonatal and infant adverse events

Clinical trials have been conducted in over 400 pregnant women using NAROPIN. These studies recorded all adverse events experienced by the baby in utero, peri- or postpartum, regardless of causality to NAROPIN, other medications or other factors.

Common events (>1%)

Cardiovascular: Foetal distress, foetal tachycardia and foetal bradycardia.

Gastrointestinal: Neonatal vomiting.

Respiratory: Neonatal respiratory disorders and neonatal tachypnoea.

Other: Neonatal fever and neonatal jaundice.

Uncommon events (<1%)

Metabolic: Foetal acidosis and neonatal hypoglycaemia.

Other: Hypotonia, neonatal sepsis and low Apgar score.

DOSAGE AND ADMINISTRATION

NAROPIN should only be used by or under the supervision of clinicians experienced in regional anaesthesia.

The presentations of NAROPIN injection solutions are intended for single use only. Any solution remaining from an opened container should be discarded.

The lowest dosage that results in effective anaesthesia should be used and should be based on the status of the patient and the type of regional anaesthesia intended. In general, surgical anaesthesia requires the use of higher concentrations and doses than those required for analgesia.

The following table is a guide to dosage. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

Adults and children above 12 years of age

RECOMMENDED DOSAGES FOR NAROPIN SOLUTION FOR VARIOUS ANAESTHETIC PROCEDURES IN THE AVERAGE, HEALTHY, 70KG ADULT PATIENT.

	%	Conc. mg/mL	Volume mL	Dose mg
SURGICAL ANAESTHESIA				
Lumbar Epidural Administration				
Abdominal, pelvic and lower limb surgery	0.75% 1%	7.5 10.0	15 - 25 15 - 20	113 - 188 150 - 200
Caesarean Section	0.75%	7.5	15 - 20	113 - 150
Thoracic Epidural Administration				
Upper abdominal and thoracic surgery	0.75%	7.5	5 - 15	38 - 113
Intrathecal Anaesthesia				
Surgery	0.5%	5.0	3 - 4	15 - 20
Field Block (incl. minor nerve blocks and infiltration)	0.75%	7.5	1 - 25	7.5 - 188
Major Nerve Block	0.75%	7.5	10 - 40	75 - 300[1]
ANALGESIA				
Lumbar Epidural Administration				
Bolus	0.2%	2.0	10 - 20	20 - 40
Intermittent injections (top-up) (e.g.) labour pain management	0.2%	2.0	10 -15 (minimum interval 30 minutes)	20 - 30
Continuous infusion (incl. labour pain and postoperative pain management)	0.2%	2.0	6 - 14 mL/h	12 - 28 mg/h

	%	Conc. mg/mL	Volume mL	Dose mg
Thoracic Epidural Administration Continuous infusion for postoperative pain management	0.2%	2.0	6 - 14 mL/h	12 - 28 mg/h
Field Block (incl. minor nerve blocks and infiltration)	0.2%	2.0	1 - 100	2 - 200
Peripheral Nerve Block (Femoral or interscalene block) Continuous infusion or intermittent injections for postoperative pain management	0.2%	2.0	5 - 10 mL/h	10 - 20 mg/h(2)
Wound Infusion (adults only) Continuous infusion via surgical wound catheter for postoperative pain management(3)	0.2%	2.0	4 – 10 mL/h	8 – 20 mg/h(2)

(1) For major nerve blocks the dosage should be adjusted to the site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with higher frequency of serious adverse reactions regardless of the local anaesthetic used.

(2) Use for up to 48 hours only.

(3) A preinfusion loading bolus dose, sufficient to fill the wound catheter and wound space is recommended. Preinfusion wound tissue infiltration should also be considered.

The appropriate concentration and volume for each procedure should be selected. The 1% (10 mg/mL) formulation is recommended for epidural anaesthesia in which a profound motor block is essential for surgery. There is no information available regarding the use of concentrations above 0.75% (7.5 mg/mL) for caesarean section. For further details of procedures please see current standard textbooks.

NOTE
Careful aspiration before and during injection is recommended to avoid intravascular injection.

Test Dose

For epidural anaesthesia, or when a large dose is to be injected, a 3 - 5 mL test dose of a local anaesthetic solution, preferably containing 5 µg/mL of adrenaline (e.g. 3 mL of Xylocaine® 2.0% with adrenaline 1:200,000) should be administered. Verbal contact and repeated monitoring of heart rate and blood pressure should be maintained for 5 minutes following the test dose after which, in the absence of signs of subarachnoid, intravascular or intrathecal injection, the main dose may be administered.

An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block.

Prior to and during administration of the total dose, aspiration should be repeated. The main dose should be injected **slowly** at a rate of 25 - 50 mg/min, while closely

observing the patient's vital functions and maintaining verbal contact. If toxic symptoms or signs occur, the injection should be stopped immediately.

Intrathecal injections should be made after the subarachnoid space has been identified and clear cerebrospinal fluid (CSF) is seen to escape from the spinal needle, or is detected by aspiration.

Analgesia

When calculating the dosage for postoperative analgesia, the use of intraoperative local anaesthetic/s should be taken into account. For treatment of postoperative pain, the following technique can be recommended:

Epidural analgesia is maintained with NAROPIN 0.2% (2 mg/mL) infusion. Infusion rates of 6 - 14 mL (12 - 28mg) per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain.

With this technique a significant reduction in the need for opioids has been observed.

Clinical experience supports the use of NAROPIN 0.2% (2 mg/mL) epidural infusions for up to 72 hours. Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections support the use for up to 48 hours only at dosages of 10 – 20 mg/hr (5 – 10 mL/hr).

When prolonged epidural blocks are used, either by continuous infusion or repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses of up to 800 mg ropivacaine for surgery and postoperative analgesia administered over 24 hours were well tolerated in adults, as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours.

When prolonged peripheral nerve blocks are applied, either through continuous infusion or through repeated injections, the risk of reaching a toxic plasma concentration or inducing local neural injury must be considered.

In clinical studies, femoral nerve block was established with 300 mg NAROPIN 0.75% (7.5 mg/mL) and interscalene block with 225 mg NAROPIN 0.75% (7.5 mg/mL), respectively, before surgery. Analgesia was then maintained with NAROPIN 0.2% (2 mg/mL). Infusion rates or intermittent injections of 10 - 20 mg per hour for 48 hours provided adequate analgesia and were well tolerated.

Use in children

Dosage Recommendations for Paediatric Patients 0 up to and including 12 Years of Age

	%	Conc. mg/mL	Volume mL/kg	Dose mg/kg
ANALGESIA				
Caudal Epidural Administration (0 – 12 years)				
Blocks below T12, in children with body weight 2.5 kg to 25 kg	0.2%	2.0	1	2
Peripheral Nerve Block (1 – 12 years)				
(e.g. ilioinguinal nerve block)	0.5%	5.0	0.4	2
Continuous Epidural Infusion (31 days – 12 years)				
In children with body weight 2.5 kg to 25 kg				
31 days up to 6 months				
Bolus dose[a]	0.2%	2.0	0.5 - 1	1 - 2
Infusion up to 72 hours	0.2%	2.0	0.1 mL/kg/h	0.2 mg/kg/h
6 to 12 months				
Bolus dose[a]	0.2%	2.0	0.5 - 1	1 - 2
Infusion up to 72 hours	0.2%	2.0	0.2 mL/kg/h	0.4 mg/kg/h
1 to 12 years				
Bolus dose[b]	0.2%	2.0	1	2
Infusion up to 72 hours	0.2%	2.0	0.2 mL/kg/h	0.4 mg/kg/h

a Doses in the low end of the dose interval are recommended for thoracic epidural blocks while doses in the high end are recommended for lumbar or caudal epidural blocks.

b Recommended for lumbar epidural blocks. It is good practice to reduce the bolus dose for thoracic epidural analgesia.

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. The volume for single caudal epidural block and the volume for epidural bolus doses should not exceed 25 mL in any patient. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

Careful aspiration before and during injection is recommended to prevent intravascular injection. The patient's vital functions should be observed closely during the injection. If toxic symptoms occur, the injection should be stopped immediately.

A single caudal epidural injection of NAROPIN 0.2% (2 mg/mL) produces adequate postoperative analgesia below T12 in the majority of patients when a dose of 2 mg/kg is used in a volume of 1 mL/kg. In children above 4 years of age,

doses up to 3 mg/kg have been used safely by the caudal route. The safety and efficacy of doses above 3 mg/kg have not been demonstrated and therefore cannot be recommended. The volume of the caudal epidural injection may be adjusted to achieve a different distribution to sensory block, as recommended in standard textbooks.

A single injection of NAROPIN 0.5% (5 mg/mL) at a dose of 2 mg/kg produces safe and effective analgesia when used for peripheral nerve block in children.

Fractionation of the calculated local anaesthetic dose is recommended, whatever the route of administration.

Use of NAROPIN in concentrations above 0.5% (5 mg/mL) have not been documented for children.

Intrathecal administration has not been documented for use in children.

The use of NAROPIN in premature children has not been documented.

Use in Debilitated or Elderly Patients

Debilitated or elderly patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction should be given reduced dosage commensurate with their physical condition. Clinical studies with this group of patients have not been performed (see PRECAUTIONS).

OVERDOSAGE

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the local anaesthetic solution (see ADVERSE EFFECTS and PRECAUTIONS).

Accidental intravascular injections of local anaesthetics may cause immediate toxic effects. Toxic effects may also arise from exceptionally rapid absorption from highly vascularised areas. In the event of overdose, peak plasma concentrations may not be reached for one to two hours, depending on the site of the injection and signs of toxicity may thus be delayed. Systemic toxic reactions may involve the central nervous system and the cardiovascular system.

In children, as in adults, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during deep sedation or general anaesthesia.

After intrathecal administration, systemic toxicity is expected to be low, due to the low dose administered. However, an excessive dose administered into the intrathecal space may give rise to total spinal block.

Contact the Poisons Information Centre for advice on management of overdose.

Symptoms

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. Initially symptoms such as visual or hearing disturbances, perioral numbness, dizziness, light headedness, tingling and paraesthesia are seen. Dysarthria, muscular rigidity and muscular twitching are more serious and may precede the onset of generalised convulsions.

Unconsciousness and grand mal convulsions may follow, which can last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly during convulsions due to the increased muscular activity, together with disruption to respiration and possible loss of functional airways. In severe cases apnoea may occur. Respiratory and metabolic acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery follows the redistribution of the local anaesthetic drug from the central nervous system and subsequent metabolism and excretion. Recovery should be rapid unless large amounts of the drug have been injected.

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics. In volunteers the intravenous infusion of NAROPIN resulted in signs of depression of conductivity and contractility.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as benzodiazepines or barbiturates. However in rare cases, cardiac arrest has occurred without prodromal CNS effects.

Treatment

If signs of acute systemic toxicity or total spinal block occur, injection of the local anaesthetic should be stopped immediately.

Treatment consists of ensuring adequate ventilation and arresting convulsions. Assisted or controlled ventilation should be maintained with oxygen, if required.

If convulsions occur and do not spontaneously stop within 15 - 20 seconds, an anticonvulsant should be given intravenously e.g. diazepam 5 - 10 mg IV or where indicated, sodium thiopentone (5 mg/kg). If convulsions interfere with breathing and/or are not rapidly controlled by specific anticonvulsant medication, suxamethonium (1 2 mg/kg) may be used to paralyse the patient. Artificial ventilation must then be instituted.

If cardiovascular depression is evident (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor and or inotropic agents should be considered. Children aged between 0 and 12 years should be given doses commensurate with their age, weight and clinical status.

If ventricular fibrillation, cardiac arrest or circulatory arrest occur, cardiopulmonary resuscitation must be instituted and maintained. Optimal oxygenation and

ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

COMPATIBILITY AND ADMIXTURES

NAROPIN solution for infusion in plastic infusion bags (Polybag) is chemically and physically compatible with fentanyl citrate, morphine sulphate and clonidine hydrochloride.

Concentration of NAROPIN: 0.1 - 0.2% (1 - 2 mg/mL)	
Additive	*Concentration*
Fentanyl citrate	1.0 - 10.0 microgram/mL
Morphine sulphate	20.0 - 100.0 microgram/mL
Clonidine hydrochloride	5.0 - 50.0 microgram/mL

Chemical and physical stability of these mixtures have been demonstrated for 30 days at up to 30°C. To reduce microbiological hazard, these admixtures should be used immediately. If not used immediately, store at 2 - 8°C for not more than 24 hours.

PRESENTATION AND STORAGE CONDITIONS

Naropin® 0.2% (2.0 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules.
100 mL, 200 mL Polybag® infusion bags.

Naropin® 0.5% (5.0 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules. (Not currently marketed.)

Naropin® 0.75% (7.5 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules.

Naropin® 1% (10.0 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules.

NAROPIN Polybag and Polyamp DuoFit presentations are in a Sterile AstraZeneca Theatre Pack™.

NAROPIN Polyamp presentations must be stored below 30°C. Do not freeze.

NAROPIN Polybag presentations must be stored below 30°C. Do not freeze.

Polybag and Polyamp must not be re-autoclaved.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription only medicine

DATE OF APPROVAL

Date of approval: 13th April 2011

5.3 Sodium Chloride Injection 0.9% Product Information

Sodium Chloride Injection 0.9%
PRODUCT INFORMATION

NAME OF THE DRUG

Chemical Name: Sodium chloride
Empirical Formula: NaCl
Molecular Weight: 58.44
CAS registry number: 7647-14-5
Structure:

Na–Cl

DESCRIPTION

Sodium Chloride Injection 0.9% is a sterile isotonic solution of sodium chloride in Water for Injections, pH 4.5 - 7.0, containing no preservatives (normal saline).

INDICATIONS

Normal saline can be used as the vehicle for many parenteral drugs and as an electrolyte replenisher for maintenance or replacement of deficits of extracellular fluid. It can also be used as a sterile irrigation medium.

CONTRAINDICATIONS

Congestive heart failure
Severe renal impairment
Conditions of sodium retention and oedema
Liver cirrhosis
Irrigation during electrosurgical procedures

PRECAUTIONS

Do not use unless the solution is clear. The entire contents of the vial, ampoule, Polyamp® or irrigation pack should be used promptly.

When used as a vehicle for intravenous drug delivery, the product information document of such drugs should be checked prior to use to ensure compatibility with the sodium chloride solution. Reconstitution instructions should be read carefully.

Excessive administration of sodium chloride causes hypernatraemia, resulting in dehydration of internal organs, hypokalaemia and acidosis. Monitoring of fluid, electrolyte and acid-base balance may be necessary. Congestive heart failure and pulmonary oedema may be precipitated, particularly in patients with cardiovascular disease or those receiving corticosteroids, corticotrophin or other drugs that may give rise to sodium retention. Sodium chloride should be administered with care to patients with congestive heart failure, hypertension, peripheral or pulmonary oedema, hypoproteinaemia, impaired renal function, urinary tract obstruction, pre-eclampsia and very young or elderly patients.

Intravenous infusion during or immediately after surgery may result in sodium retention.

Given that there is a possibility of systemic absorption of irrigation solutions, the same precautions apply.

Use in pregnancy
Safety in pregnancy has not been established. Use is recommended only when clearly indicated.

Use in lactation
Safety in lactation has not yet been established. Use of this product whilst breastfeeding is recommended only when potential benefits outweigh potential risks to the newborn.

Interactions with other drugs
Additives may be incompatible with sodium chloride.
Co medication of drugs inducing sodium retention may exacerbate any systemic effects.

ADVERSE REACTIONS

Excessive amounts of sodium chloride may cause hypernatraemia, hypokalaemia and acidosis. Proper use of normal saline as a vehicle for parenteral drugs or as an electrolyte replacement therapy is unlikely to result in adverse effects.

Hypernatraemia rarely occurs with therapeutic doses of sodium chloride, but may occur in excessive administration. A serious complication of this is dehydration of the brain causing somnolence and confusion, which may progress to convulsions, coma and ultimately respiratory failure and death. Pulmonary embolism or pneumonia may also result. Other symptoms include thirst, reduced salivation and lacrimation, fever, tachycardia, hypertension, headache, dizziness, restlessness, weakness and irritability.

If any adverse effects are observed during administration, discontinue infusion, evaluate the patient and institute appropriate supportive treatment.

Displaced catheters or drainage tubes can lead to irrigation or infiltration of unintended structures or cavities. Excessive volume or pressure during irrigation of closed cavities may result in distension or disruption of tissues. Inadvertent contamination from careless technique may transmit infection. Adverse effects resulting from irrigation of body cavities, tissues or indwelling catheters and tubes are usually avoidable when appropriate procedures are followed.

DOSAGE AND ADMINISTRATION

The dosage of sodium chloride as a vehicle for parenteral drugs and as an electrolyte replenisher must be calculated after consideration of clinical and laboratory data.

OVERDOSAGE

Excess sodium chloride in the body produces general gastrointestinal effects of nausea, vomiting, diarrhoea and cramps. Salivation and lacrimation are reduced, while thirst and sweating are increased. Hypotension, tachycardia, renal failure, peripheral and pulmonary oedema and respiratory arrest may occur. CNS symptoms include headache, dizziness, restlessness, irritability, weakness, muscular twitching and rigidity, convulsions, coma and death.

Treatment

Normal plasma sodium concentrations should be carefully restored at a rate not greater than 10 - 15 mmol/day using IV hypotonic saline. Dialysis may be necessary if there is significant renal impairment, the patient is moribund or plasma sodium levels are greater than 200 mmol/L. Convulsions are to be treated with IV diazepam.

PRESENTATION

Sodium Chloride Injection 0.9% glass ampoules (not marketed)

2 mL ampoules in packs of 5 and 50
5 mL ampoules in packs of 5, 10 and 50
10 mL ampoules in packs of 10 and 50

Sodium Chloride Injection 0.9% Polyamp DuoFit® polyethylene ampoules

2 mL ampoules in packs of 5 and 50 (not marketed)
5 mL ampoules in packs of 5, 10 and 50
10 mL ampoules in packs of 10, 30, 50 and 400

STORAGE

Glass ampoules (not marketed)

2 mL – store below 25°C
5 mL – store below 30°C
10 mL – store below 30°C

Polyamp DuoFit®

2 mL – store below 25°C (not marketed)
5 mL – store below 25°C
10 mL – store below 30°C

POISONS SCHEDULE

Unscheduled

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road, North Ryde
NSW 2113 Australia

Date of safety related notification: 22 May 2003
Date of most recent amendment: 13 March 2013

5.4 On-Q Painbuster Product Information

ON-Q® PainBuster®

For less pain after surgery and faster recovery for your patients

Pain Control

B|BRAUN
SHARING EXPERTISE

ON-Q® PainBuster®

For less pain after surgery and faster recovery for your patients – ON-Q® PainBuster®

With ON-Q® PainBuster® you are redefining recovery
Continuous wound infiltration is a technique that delivers local anesthetic through a multi-holed catheter directly into the surgical site for post operative pain relief.

With ON-Q® and continuous wound infiltration, you may expect:

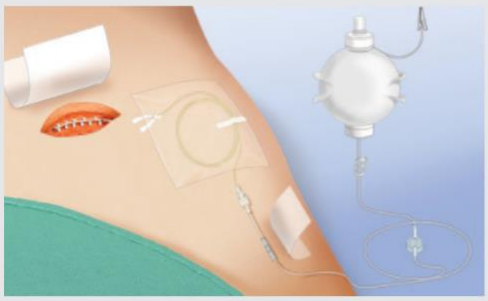
- Quicker return to normal, including ambulation, body functions, and full range of motion[1]
- Decreased complications associated with narcotics – such as respiratory depression, nausea, vomiting, dizziness and constipation[1]
- Clinically proven success – used in thousands of surgeries[1]
- Over 90 % patient satisfaction[1]
- 1 to 3 fewer days in the ICU or hospital[1]
- Up to 30 % reduction in treatment costs[2]

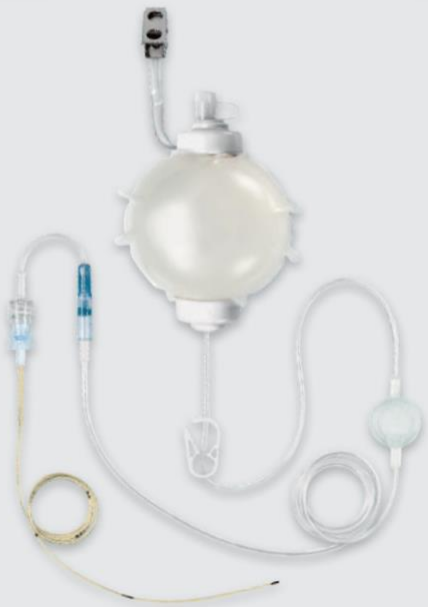
User benefits

- Reduced hospital stays
- Significantly less narcotics
- Simplicity – no electronics, no maintenance
- Reduction in treatment costs

1 Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of Continuous Wound Catheters Delivering Local Anaesthetic for Postoperative Analgesia: A Quantitative and Qualitative Systematic Review of Randomized Controlled Trials. JACS 2006; 203(6): 914-932.

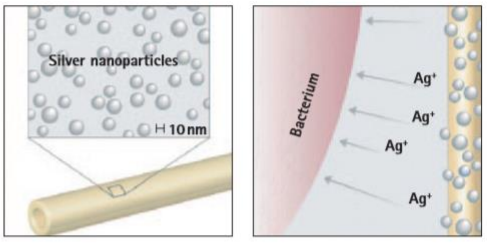
2 Zimberg S, Reducing Pain and Costs with Innovative Postoperative Pain Management, Managed Care Quarterly 2003; 11(1): 34-36 .





Soaker Catheter™ features and benefits:

- Unique catheter design with multiple lateral holes along the infusion segment
- No wicking effect to ensure an even distribution
- Wide range of catheter saturation lengths
- Easy to use introducer needle with peel-away sheath
- Length markings for more accurate positioning
- Dual catheter systems available
- Catheter is treated with a specially formulated antimicrobial silver agent that may destroy or inhibit the growth of micro organisms on the inner and outer surface of the catheter (only SilverSoaker™)



Bacterium attacked by silver ions (Ag+s) released by SilvaGard®

ON-Q® SilverSoaker™
Antimicrobial Catheter

ON-Q® Soaker Catheter™

ON-Q® PainBuster® –
For Better Patient Outcome

Product Specifications

PainBuster®										
Delivery Time Days[3]	Fill Volume (ml)	Flow Rate (ml/h)	Catheter 1 in (2.5 cm)		Catheter 2.5 in (6.5 cm)		Catheter 5 in (12.5 cm)		Catheter 10 in (25 cm)	
			Soaker Catheter™	Silver Soaker™	Soaker Catheter™	Silver Soaker™	Soaker Catheter™	Silver Soaker™	Soaker Catheter™	Silver Soaker™
4	100	1	5001790	–	–	–	–	–	–	–
2	100	2	5001489	–	5001258	5001656	5001473	–	–	–
5	270	2	–	–	5001259	5001793	5001474	–	–	–
2 1/4	270	5	5001490	–	5001260	5001657	5001302	5001659	–	–
3	270	4 (2x2)	–	–	5001275	5001658	5001475	5001660	5001679	5001796
3 1/2	400	5	–	–	5001825	–	5001456	5001794	5001680	5001797
2	400	10	–	–	5001823	–	5001457	–	–	–
4	400	4 (2x2)	–	–	5001455	–	5001458	5001795	–	–

[3] Delivery time is approximate and based on nominal specifications. See Instructions For Use for complete product information.

All cases include 5 PainBuster® kits and each kit includes:

- Infusion pump
- 60 ml filling syringe
- E-clip or carry case
- Soaker Catheter(s)™
- 17G T-peel introducer(s) and sheath(s)
- 5 ml priming syringe
- Medication label
- Peel-Away labels
- Patient guidelines
- Instructions for use
- Filling extension set - 400 ml models only

Expansion Kits[4]	Code No. (REF)
ON-Q® Soaker Catheter™ 2.5 cm (1")	5001731
ON-Q® Soaker Catheter™ 6.5 cm (2.5")	5001729
ON-Q® Soaker Catheter™ 12.5 cm (5")	5001730
ON-Q® Soaker Catheter™ 25 cm (10")	5001732
ON-Q® SilverSoaker™ 2.5 cm (1")	5001710
ON-Q® SilverSoaker™ 6.5 cm (2.5")	5001708
ON-Q® SilverSoaker™ 12.5 cm (5")	5001709
ON-Q® SilverSoaker™ 19.1 cm (7.5")	5001818
ON-Q® SilverSoaker™ 25 cm (10")	5001711

[4] Contents: Soaker catheter(s), T-peel needle(s), 5cc priming syringe, Tegaderm™ and Steri-Strips™

PainBuster® Accessories

PainBuster® Accessories	Code No. (REF)
Soaker introducer needle 3.25" (8.3 cm)	5001402
Soaker introducer needle 6" (15.2 cm)	5001430
Soaker introducer needle 8" (20.3 cm)	5001429
Filling extension set	5001439
Multi-Ad® Fluid Dispensing System (filling aid)	513506
Multi-Ad® Set (filling aid)	513548

Disposable Tunnelers[5]	Code No. (REF)
Disposable tunneler 3.25" (8.25 cm), 17G	5001685
Disposable tunneler 5" (12.5 cm), 17G	5001687
Disposable tunneler 8" (20.3 cm), 11G	5001763
Disposable tunneler 8" (20.3 cm), 17G	5001689
Disposable tunneler 12" (30.5 cm), 11G	5001765
Disposable tunneler 12" (30.5 cm), 16G	5001761

[5] Contents: Tunneler and two disposable sheaths

⚠ **Warning:**
Avoid placing the catheter in joint spaces. Although there is no definitive established causal relationship, some literature has shown a possible association between continuous intra-articular infusions (particularly with bupivacaine) and the subsequent development of chondrolysis.

B. Braun Melsungen AG | Hospital Care | 34209 Melsungen | Germany
Tel. +49 5661 71-0 | www.bbraun.com

B. 03. 05. 10/1 Nr. 6069103

5.5 Participant Case File Information Sheet

AFFIX PATIENT ID STICKER HERE

This patient is a participant in the Intraperitoneal Local Anaesthetic (IPLA) in Bowel Surgery Clinical Trial

WHAT DOES THIS MEAN?

- For 48 hours after their surgery the patient will wear a painbuster pump with catheter inserted into the peritoneal cavity (abdomen)
- They will be receiving an infusion of either 0.2% ropivacaine or normal saline at 10ml/hr.
- When their vital signs are recorded they should also be screened for ropivacaine toxicity using the questions on the chart provided to nursing staff.
- They are required to complete a patient diary that records their pain and recovery at set times following the operation.
- Other than that, there should be no change to the management of this patient following their bowel surgery.

SAFETY CONSIDERATIONS - WHEN SHOULD I BE CONCERNED?

Severe to life threatening side effects of ropivacaine are similar to those observed with any local anaesthetic agent. Toxicity, anaphylaxis or cardiac arrest may result from overdosage, accidental intravenous injection, or altered absorption or metabolism of the drug.

- If the patient reports:
  - Tingling or numbness of mouth and tongue
  - Inability to properly form words while speaking
  - Light-headedness
  - Muscle twitching

Then the painbuster catheter clamp should be closed and a medical officer review initiated.

- If nursing or medical staff directly observe muscle twitching, or for any reason ECG changes are noted, then the painbuster catheter clamp should be closed and a Medical Emergency Response (MER) call for immediate medical officer review should be made.
- At medical officer review, if any adverse sign or symptom is suspected to be the result of ropivacaine infusion, **ensure the painbuster catheter clamp is closed so the infusion has ceased** and implement further investigation and management, such as transfer to a monitored bed.

THERE IS A MEDICAL EMERGENCY, WHAT SHOULD I DO?

- **Close the painbuster catheter clamp to cease the infusion**
- **Ensure that a Medical Emergency Response (MER) call has been made.**
  - Clinical Trial Advice is available 24hrs by phoning Dr Jaime Duffield 0418329970.
  - Emergency unblinding is available by calling Peter Slobodian, Clinical Pharmacist, via Royal Adelaide Hospital switchboard 82224000.

FOR SAFETY, THIS CLINICAL DOCUMENT MUST BE KEPT ON THE FRONT OF BOTH THE PARTICIPANTS CASE FILE AND OBSRVATION CHART WHILE THE TRIAL INFUSION IS RUNNING

5.6 Ropivacaine Toxicity Screening Chart

AFFIX PATIENT ID STICKER HERE

Clinical Trial : Intraperitoneal Local Anaesthetic (IPLA) in Bowel Surgery

ROPIVACAINE TOXICITY SCREENING CHART

This chart must be kept with the standard observations chart and completed by nursing staff.

Please ask these routine screening questions 3 hourly for the first 6 postoperative hours and then with your routine vital sign observations for the remainder of the 48 hr infusion.

DATE														
TIME														
1. Do you feel lightheaded? Yes/No														
2. Have you experienced any numbness or tingling of your mouth or tongue? Yes/No														
3. Have you noticed any muscle twitching? Yes/No														
I have checked with my patient that their study diary is up to date.														

- **If the patient answers "YES" to any of questions 1, 2 or 3** close the painbuster catheter clamp to stop the infusion and phone Dr Duffield .
- If you directly observe muscle twitching, or for any reason ECG changes are noted, then close the painbuster catheter clamp to stop the infusion and initiate a Medical Emergency Response (MER) call for immediate medical officer review.
- At medical officer review, ensure the medical officer is made aware of the trial and the information sheet at the front of the patients' case file.

- Clinical Trial Advice is available 24hrs a day by phoning [redacted] Dr Jaime Duffield.

Upon completion of this clinical documentation please retain in the participants case file.

5.7 Participant Diary

AFFIX PATIENT STICKER HERE

Intraperitoneal Local Anaesthetic Study

Royal Adelaide Hospital

Participant Inpatient Diary

Your operation ended and infusion started on:

Date:

Time:

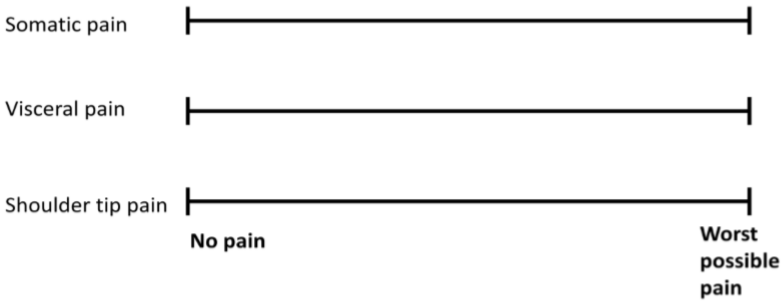
Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 3 hours postoperation (date: time:)

Please rate your postoperative pain for each of

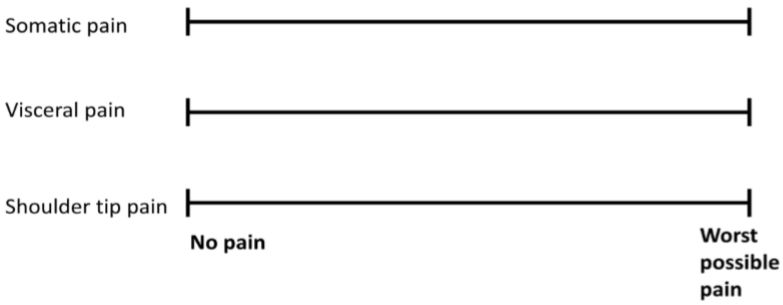
I. somatic pain (incisional pain in the abdominal wall that can be touched)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain



At 6 hours postoperation (date: time:)

Please rate your postoperative pain for each of

I. somatic pain (incisional pain in the abdominal wall that can be touched)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain



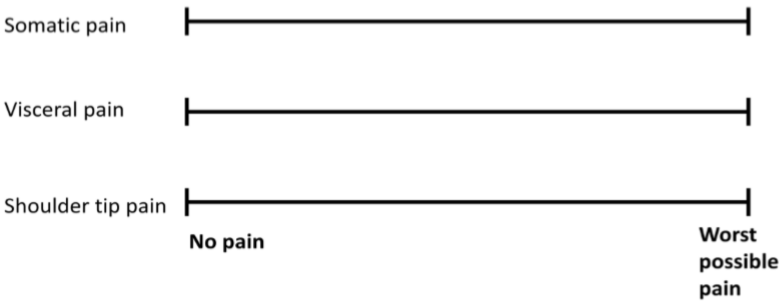
Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 12 hours postoperation (date: time:)

Please rate your postoperative pain for each of

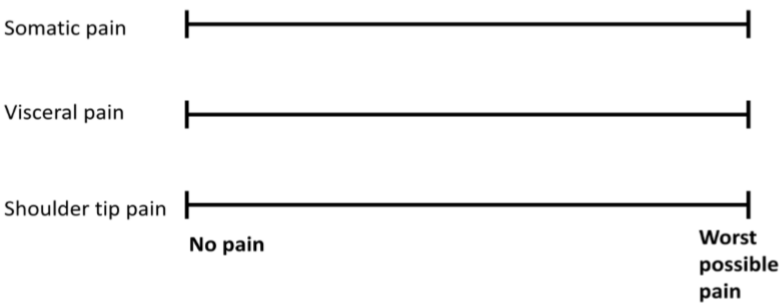
I. somatic pain (incisional pain in the abdominal wall that can be touched)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain



At 24 hours postoperation (date: time:)

Please rate your postoperative pain for each of

I. somatic pain (incisional pain in the abdominal wall that can be touched)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain



and separately complete the Surgical Recovery Scale on the next page.

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 24 hrs post operation please complete the Surgical Recovery Scale below.
Date: Time:

Please think about the **last two days** and tick the box that applies best to you.

During the last two days …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
1. I have been feeling energetic						
2. I have been feeling worn out						
3. I have been feeling vigorous						
4. I have done very little with the day						
5. I have been feeling fatigued						
6. Physically, I have felt tired						
7. I have had to restrict how much I try and do in a day						
8. I have been feeling lively						

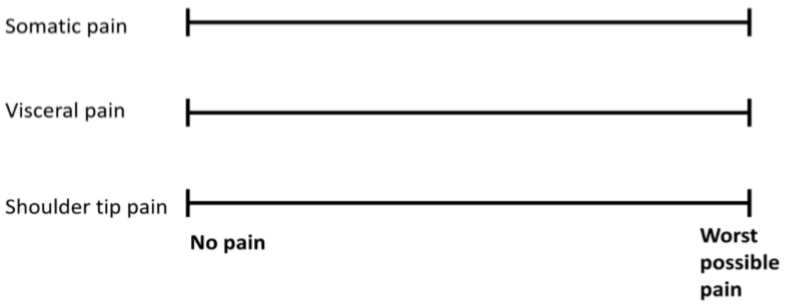
During the last two days, I have been able to…	Not at all ▼	Only occasionally ▼	Sometimes, but less than usual ▼	Nearly as often as usual ▼	As often as usual ▼	Not applicable to me ▼
9. Read a newspaper/book or watch TV						
10. Dress						
11. Visit or socialize with family and friends						
12. Engage in leisure or recreational activities						
13. Shop or do errands						

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

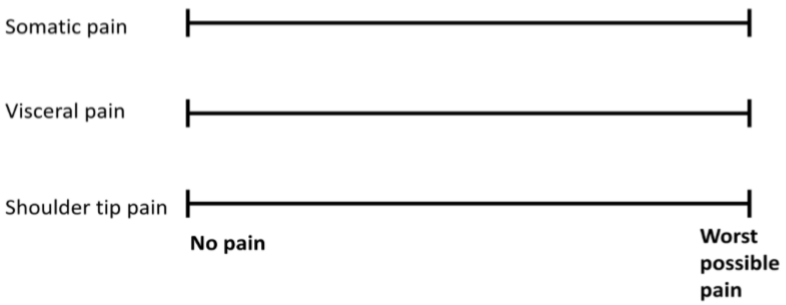
At 48 hours postoperation (date: time:)

Please rate your postoperative pain for each of
I. somatic pain (incisional pain in the abdominal wall that can be touched)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain



At 72 hours postoperation (date: time:)

Please rate your postoperative pain for each of
I. somatic pain (incisional pain in the abdominal wall that can be touched)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain



and separately complete the Surgical Recovery Scale on the next page.

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 72 hours post operation please complete the Surgical Recovery Scale below.
Date: Time:

Please think about the **last two days** and tick the box that applies best to you.

During the last two days …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
1. I have been feeling energetic						
2. I have been feeling worn out						
3. I have been feeling vigorous						
4. I have done very little with the day						
5. I have been feeling fatigued						
6. Physically, I have felt tired						
7. I have had to restrict how much I try and do in a day						
8. I have been feeling lively						

During the last two days, I have been able to…	Not at all ▼	Only occasionally ▼	Sometimes, but less than usual ▼	Nearly as often as usual ▼	As often as usual ▼	Not applicable to me ▼
9. Read a newspaper/book or watch TV						
10. Dress						
11. Visit or socialize with family and friends						
12. Engage in leisure or recreational activities						
13. Shop or do errands						

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

I drank my first drink and kept it down:

Date: ..... Time: .....

I ate my first meal and kept it down:

Date: ..... Time: .....

I passed wind for the first time:

Date: ..... Time: .....

I opened my bowels for the first time:

Date: ..... Time: .....

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

Thank you for completing your participant inpatient diary

Please hand this section of your participant diary to your nurse so it can be retained in your permanent patient record.

On discharge from hospital please take the remaining section of your participant diary home for completion.

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

Intraperitoneal Local Anaesthetic Study

Royal Adelaide Hospital

Participant Outpatient Diary

Your operation ended and infusion started on:

Date:

Time:

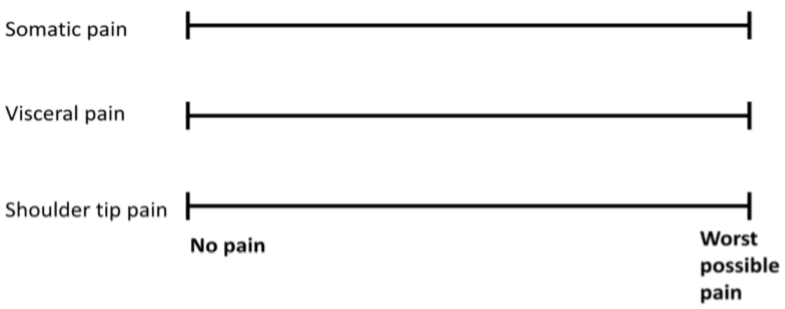
Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 7 days postoperation (date: time:)

Please rate your postoperative pain for each of

I. somatic pain (incisional pain in the abdominal wall that can be touched)
II. visceral pain (deep, dull, inside the abdomen)
III. shoulder tip pain



and separately complete the Surgical Recovery Scale on the next page.

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 7 days post operation please complete the Surgical Recovery Scale below.
Date: Time:

Please think about the **last two days** and tick the box that applies best to you.

During the last two days …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
1. I have been feeling energetic						
2. I have been feeling worn out						
3. I have been feeling vigorous						
4. I have done very little with the day						
5. I have been feeling fatigued						
6. Physically, I have felt tired						
7. I have had to restrict how much I try and do in a day						
8. I have been feeling lively						

During the last two days, I have been able to…	Not at all ▼	Only occasionally ▼	Sometimes, but less than usual ▼	Nearly as often as usual ▼	As often as usual ▼	Not applicable to me ▼
9. Read a newspaper/book or watch TV						
10. Dress						
11. Visit or socialize with family and friends						
12. Engage in leisure or recreational activities						
13. Shop or do errands						

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 30 days post operation please complete the Surgical Recovery Scale below.
Date: Time:

Please think about the **last two days** and tick the box that applies best to you.

During the last two days …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
1. I have been feeling energetic						
2. I have been feeling worn out						
3. I have been feeling vigorous						
4. I have done very little with the day						
5. I have been feeling fatigued						
6. Physically, I have felt tired						
7. I have had to restrict how much I try and do in a day						
8. I have been feeling lively						

During the last two days, I have been able to…	Not at all ▼	Only occasionally ▼	Sometimes, but less than usual ▼	Nearly as often as usual ▼	As often as usual ▼	Not applicable to me ▼
9. Read a newspaper/book or watch TV						
10. Dress						
11. Visit or socialize with family and friends						
12. Engage in leisure or recreational activities						
13. Shop or do errands						

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

At 45 days post operation please complete the Surgical Recovery Scale below.
Date: Time:

Please think about the **last two days** and tick the box that applies best to you.

During the last two days …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
1. I have been feeling energetic						
2. I have been feeling worn out						
3. I have been feeling vigorous						
4. I have done very little with the day						
5. I have been feeling fatigued						
6. Physically, I have felt tired						
7. I have had to restrict how much I try and do in a day						
8. I have been feeling lively						

During the last two days, I have been able to…	Not at all ▼	Only occasionally ▼	Sometimes, but less than usual ▼	Nearly as often as usual ▼	As often as usual ▼	Not applicable to me ▼
9. Read a newspaper/book or watch TV						
10. Dress						
11. Visit or socialize with family and friends						
12. Engage in leisure or recreational activities						
13. Shop or do errands						

Upon completion of this clinical documentation please retain in the participants case file.

AFFIX PATIENT STICKER HERE

Thank you for completing your participant outpatient diary

Please mail this section of your participant diary to

Dr Jaime Duffield
C/O Surgical Specialities
Level 5 North Wing
Royal Adelaide Hospital
North Terrace SA 5000

In the envelope provided in your pack, or scan and email to
colorectalsurgeryresearch@gmail.com

Or phone 8222 4000 and ask to speak to Dr Jaime Duffield to arrange an alternative collection.

Upon completion of this clinical documentation please retain in the participants case file.

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