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Prospective randomized, double-blind, placebo-controlled study of pre- and postoperative administration of a COX-2-specific inhibitor as opioid-sparing analgesia in major colorectal resections

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Introduction

- Postoperative ileus (POI) is a problem
- POI is inflammatory in origin[1]
- Pain relief is another problem
- Opioids and POI

1. Kreiss C, Birder LA, Kiss S, et al. COX-2 dependent inflammation increases spinal Fos expression during rodent postoperative ileus. Gut 2003 Apr; 52(4):527-34.

Hypothesis

- Patients treated with Valdecoxib, a COX-2-specific inhibitor, will have reduced postoperative ileus and a shorter recovery when compared with a standard postoperative patient-controlled analgesia (PCA) morphine only regimen after colorectal resections.

Aims

- Demonstrate the reduction of postoperative ileus and opioid-sparing effect with the use of a COX-2-specific inhibitor administered pre- and post-operatively in patients undergoing major colorectal surgery.

Patients and Methods

- One institution from Dec 2002 to Jun 2004
- Randomized, double-blind, placebo-controlled
- In the study arm, the first dose of Valdecoxib 40mg was administered orally as close to one hour prior to the start of surgery. Each subsequent dose was administered at 24-hour intervals up to 120h.
- Patients in the control arm were served placebos at the same timings.

Patients and Methods

- The primary endpoint for calculating sample size was days to first bowel movement.
- A sample size of 40 patients per group is sufficient to detect a difference of 1 day (25%, assuming average 4 days to first bowel movement) with at least 80% power and type I error of 0.025 (for a two-sided test adjusted for two treatment comparisons).

Patients and Methods

Inclusion Criteria:

The patient is a male or female of more than 18 years of age and

- requires elective colorectal resection including cancers
- is in satisfactory health as determined by the Investigator on the basis of medical history and physical examination
- ASA class I-III
- is able to use PCA
- has provided written informed consent prior to admission to this study

Patients and Methods

Exclusion Criteria:

The patient

- has sulfonamide allergy.
- requires emergency surgery / laparoscopic assisted surgery
- has inflammatory bowel disease
- needs epidural or other regional analgesia
- has known opioid intolerance or inability to use PCA
- has known acetylsalicylic acid or NSAIDs hypersensitivity
- has active peptic ulcer disease, asthma, coagulopathy, or renal failure
- is pregnant or lactating
- uses conventional NSAIDs, COX-2 inhibitors, or tramadol during the six hours preceding surgery, during surgery or subsequent to the end of surgery
- is required to take muscle relaxants, tricyclic antidepressants, tranquilizers, sedatives, hypnotics or neuroleptics in the postoperative period

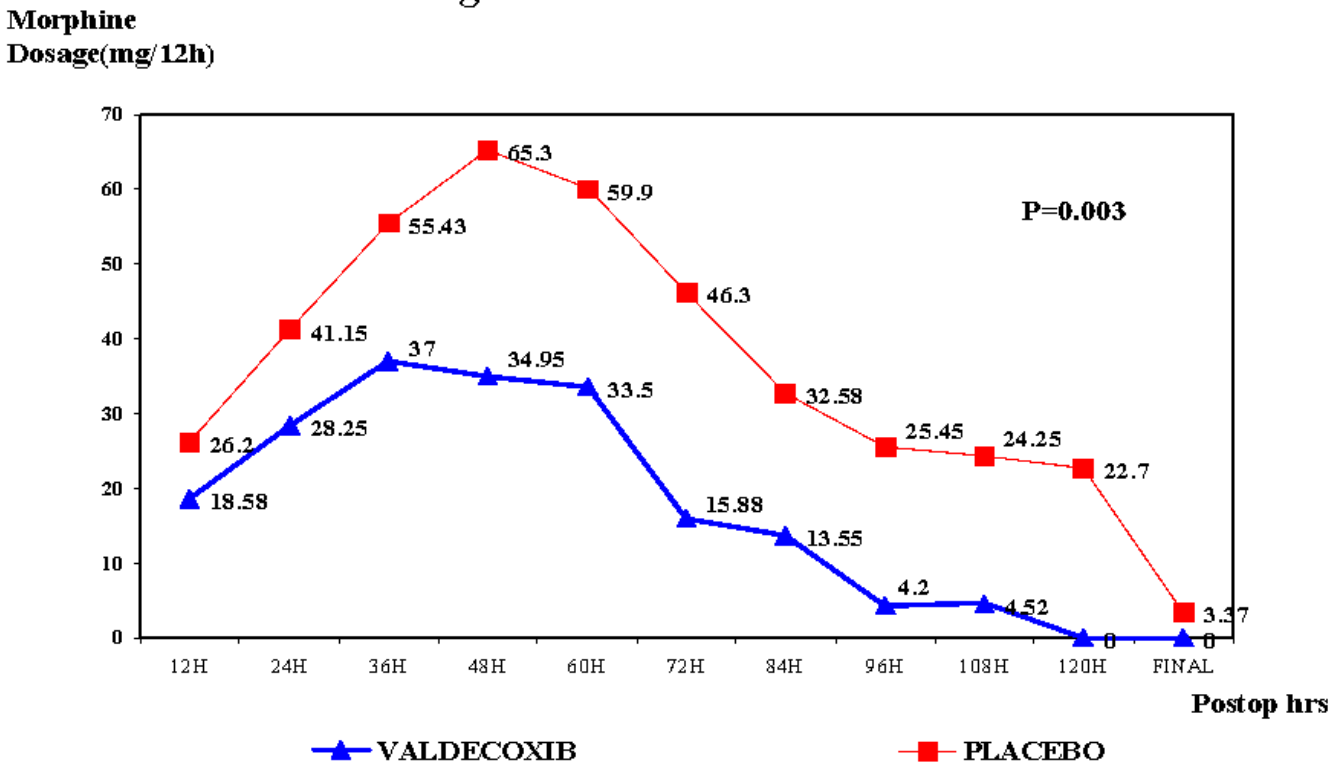
Patients and Methods

- PCA morphine was used for analgesia uniformly and stopped when there was adequate analgesia with Paracetamol 1g p.o. q6hr prn.
- Pain assessments completed after resting supine for at least 15 minutes.
- Clear liquid diet on the POD1. Once oral intake exceeds 30ml/kg of body weight without nausea or vomiting, diet was advanced to a low-fat, gastrointestinal diet.
- Evaluated every 12 hours, once in the morning and again in the evening for the endpoints of bowel sound, flatus and bowel movement.
- Discharged when 1) tolerating a solid diet, 2) passing flatus, 3) without fever or other medical problem requiring hospitalisation.

Patient characteristic	Study (n = 40)	Placebo (n = 39)	P
Age (years)			
Mean (SD)	61.0 (11.4)	63.1 (10.4)	0.585
Range	24 - 77	39 - 78	
Sex Male	20 (50.0%)	18 (46.0%)	0.654
Female	20 (50.0%)	21 (54.0%)	
Medical Problems* (COAD, Hypt, DM, IHD)			
Yes	26 (65.0%)	24 (62.0%)	0.777
No	14 (35.0%)	15 (38.0%)	
BMI Mean (SD)	23.0 (3.7)	23.0 (3.7)	0.511
Range	17.8 - 33.2	16.0 - 33.0	
Diagnosis			
Colorectal cancer	36 (90.0%)	39 (100.0%)	0.136
Benign (sigmoid diverticulitis, sigmoid volvulus)	4 (10.0%)	0	

Patient characteristic	Study (n = 40)	Placebo (n = 39)	P
Type of Operation			
Anterior Resection (AR)	15 (37.5%)	16 (41.0%)	0.158
AR (with extended resection)	6 (15.0%)	2 (5.1%)	
Low AR	4 (10.0%)	4 (10.2%)	
Low AR with stoma	3 (7.5%)	1 (2.6%)	
Hartmann's Procedure	3 (7.5%)	0	
Abdomino-Perineal Resection	1 (2.5%)	4 (10.0%)	
Hemicolectomy	5 (12.5%)	11 (28.2%)	
Others (small bowel resection, panprotocolectomy, Hartmann's reversal)	3 (7.5%)	1 (2.6%)	
Stoma - Yes	8 (20.0%)	5 (12.8%)	0.405
No	32 (80.0%)	34 (87.2%)	
Incision Length (cm)			
Mean (SD)	17.8 (11.1)	17.0 (4.2)	0.436
Range	10 - 25	7 - 28	
Duration of Operation (min)			
Mean (SD)	158.0 (61.1)	152.0 (55.3)	0.733
Range	65 – 320	75 – 300	

Fig. 1 - PCA Dose-Mean



30% reduction at 24h, 45% reduction at 48h

Fig.2 - PCA Dose - Total

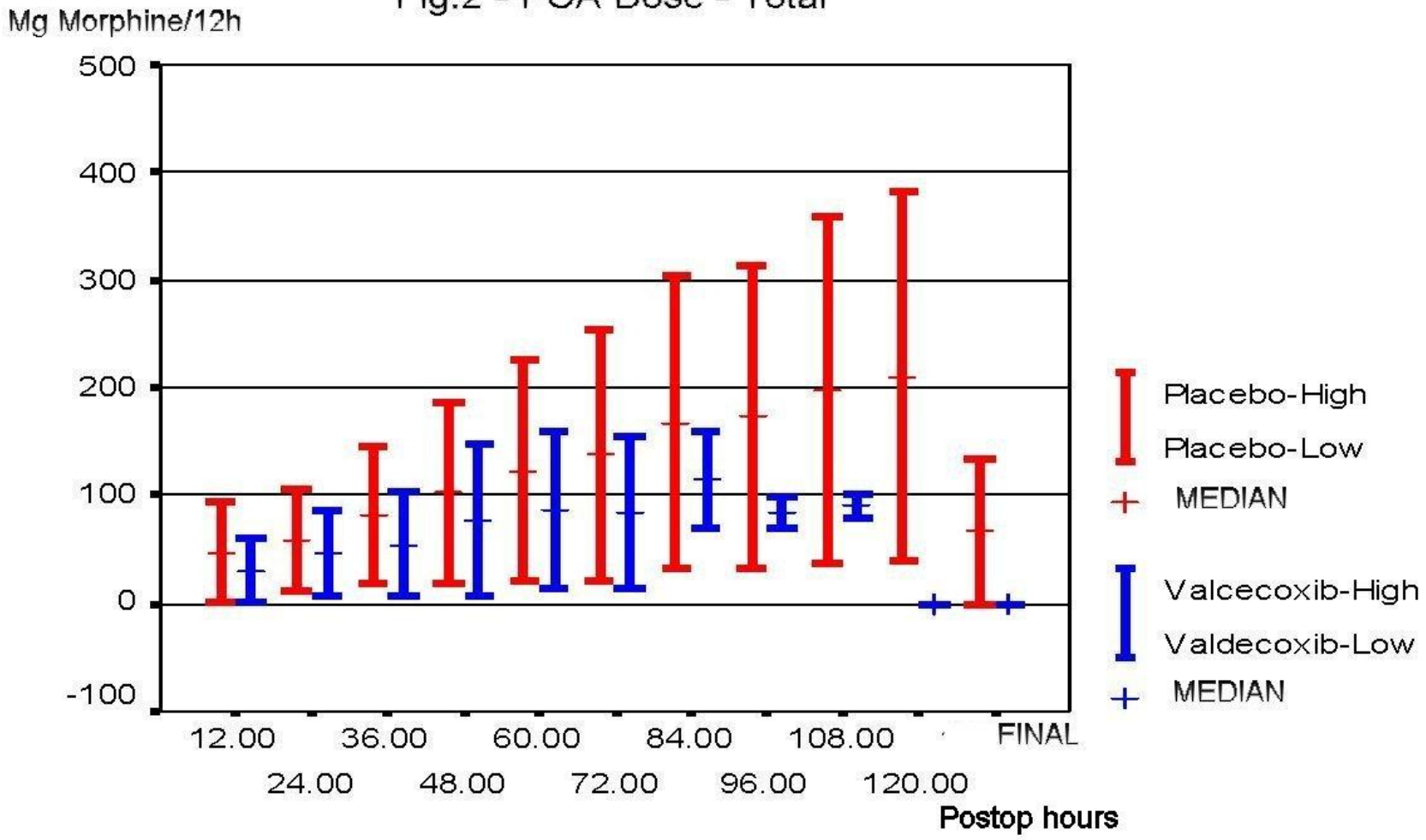
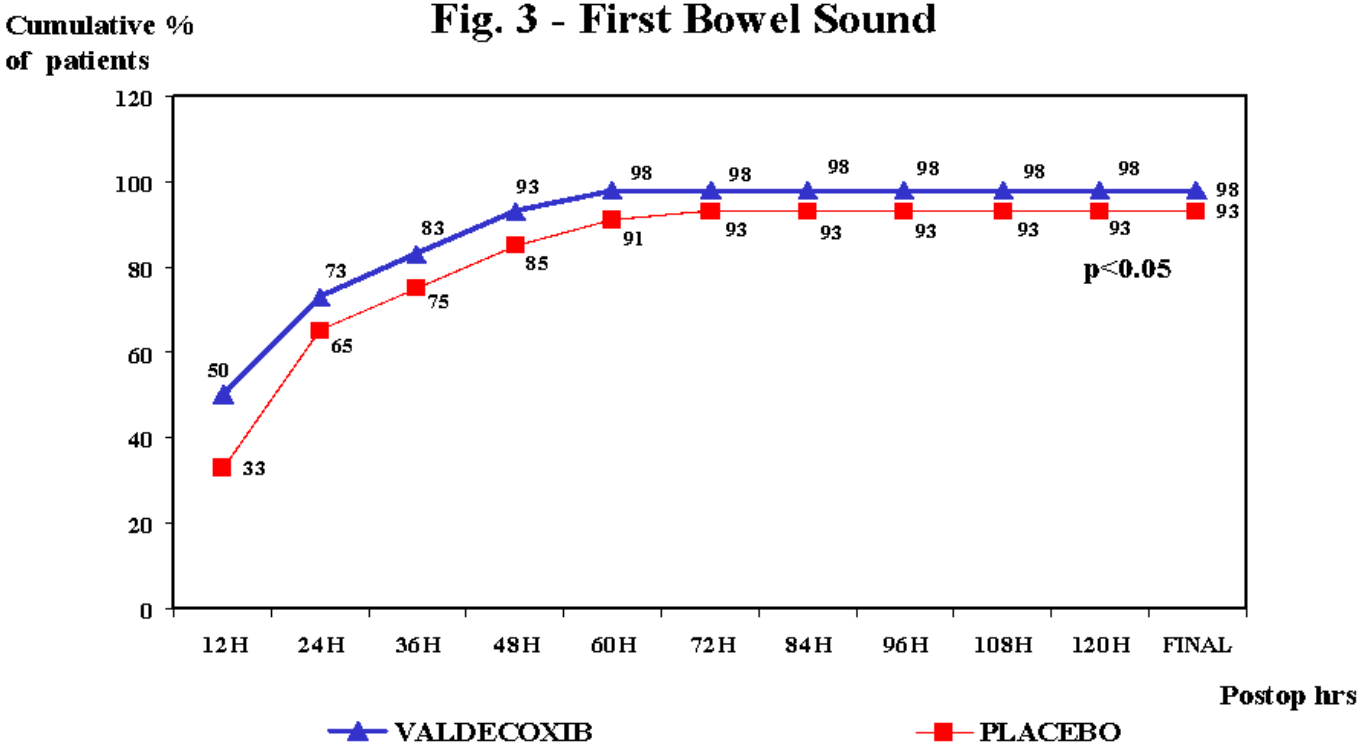
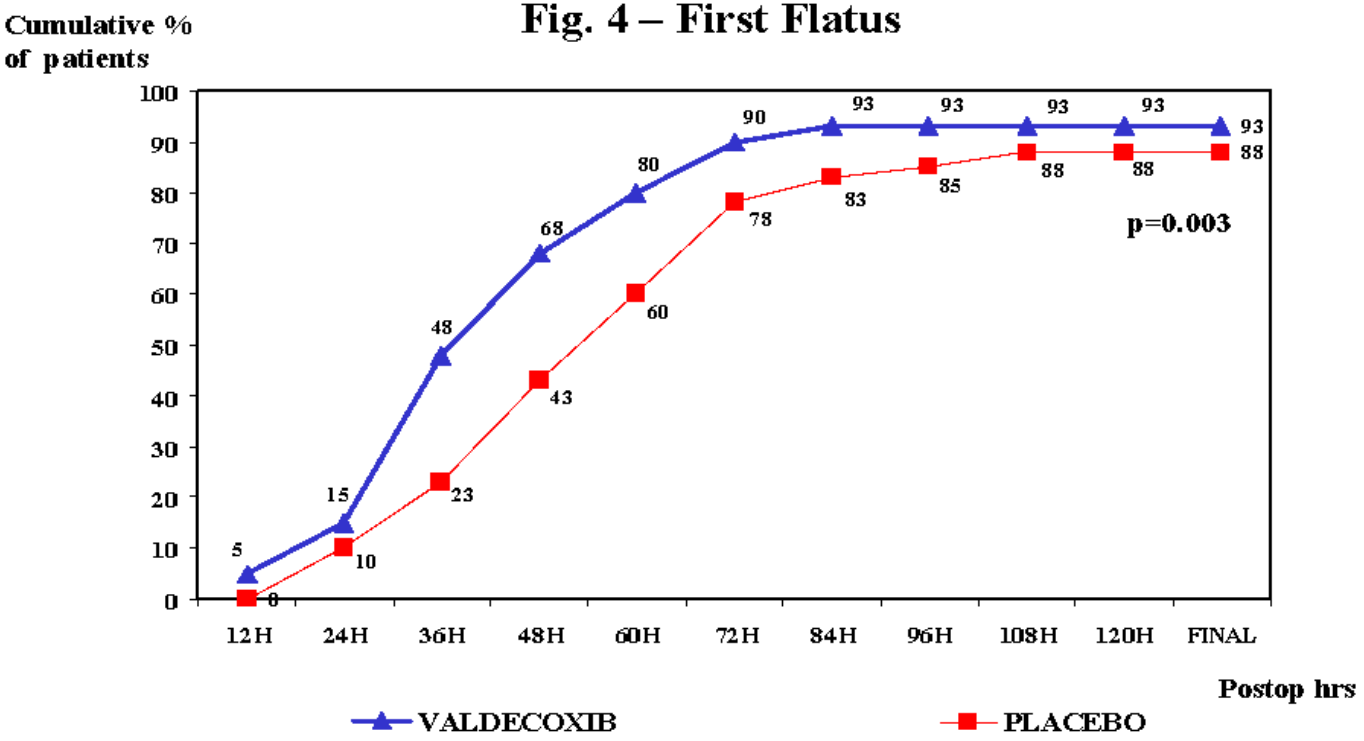


Fig. 3 - First Bowel Sound



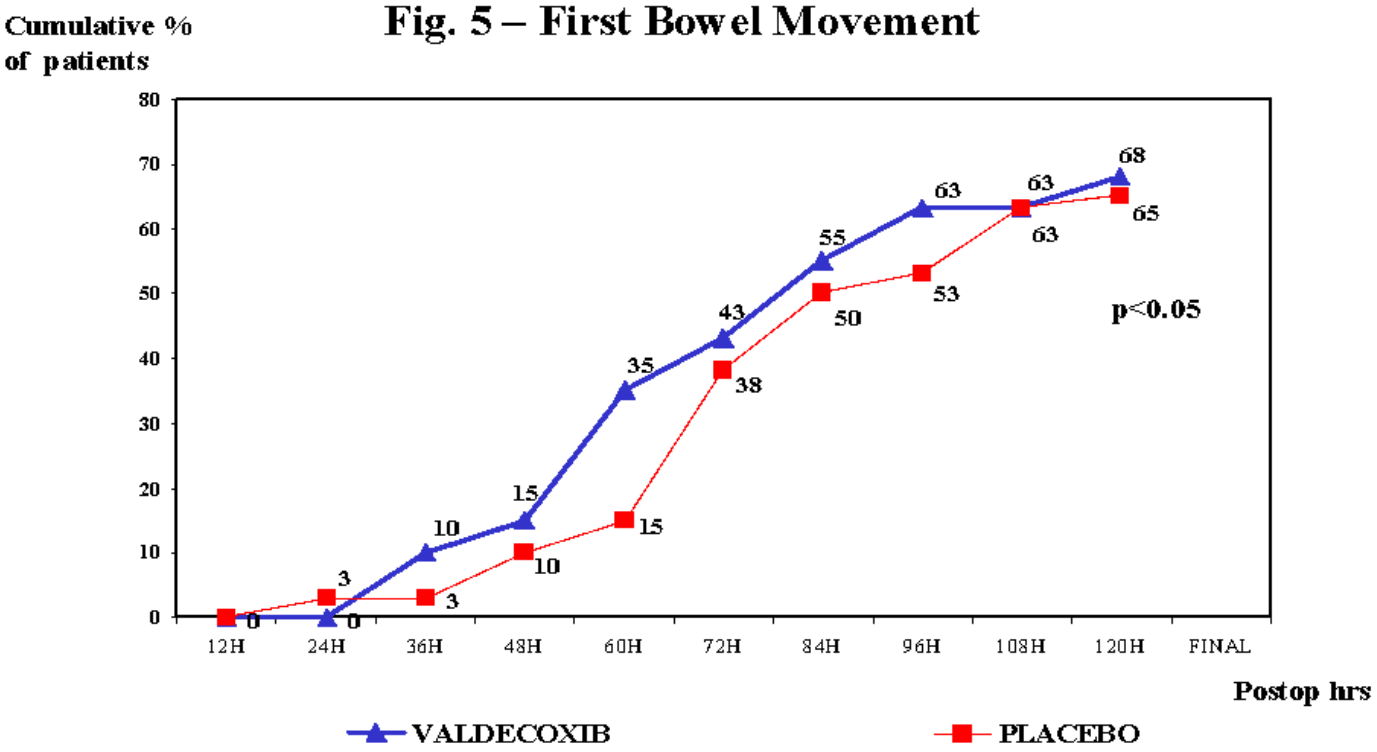
Median 12h vs 24h

Fig. 4 – First Flatus

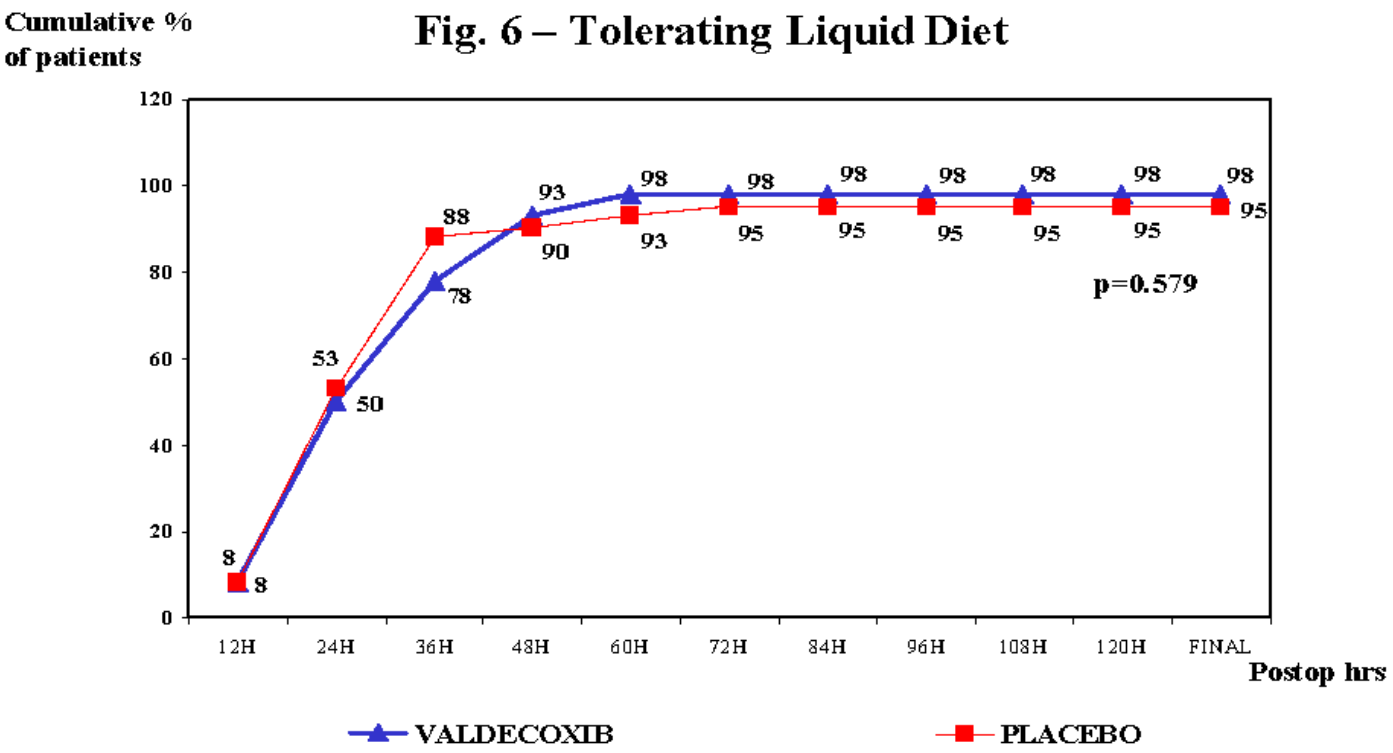


Median 36h vs 48h

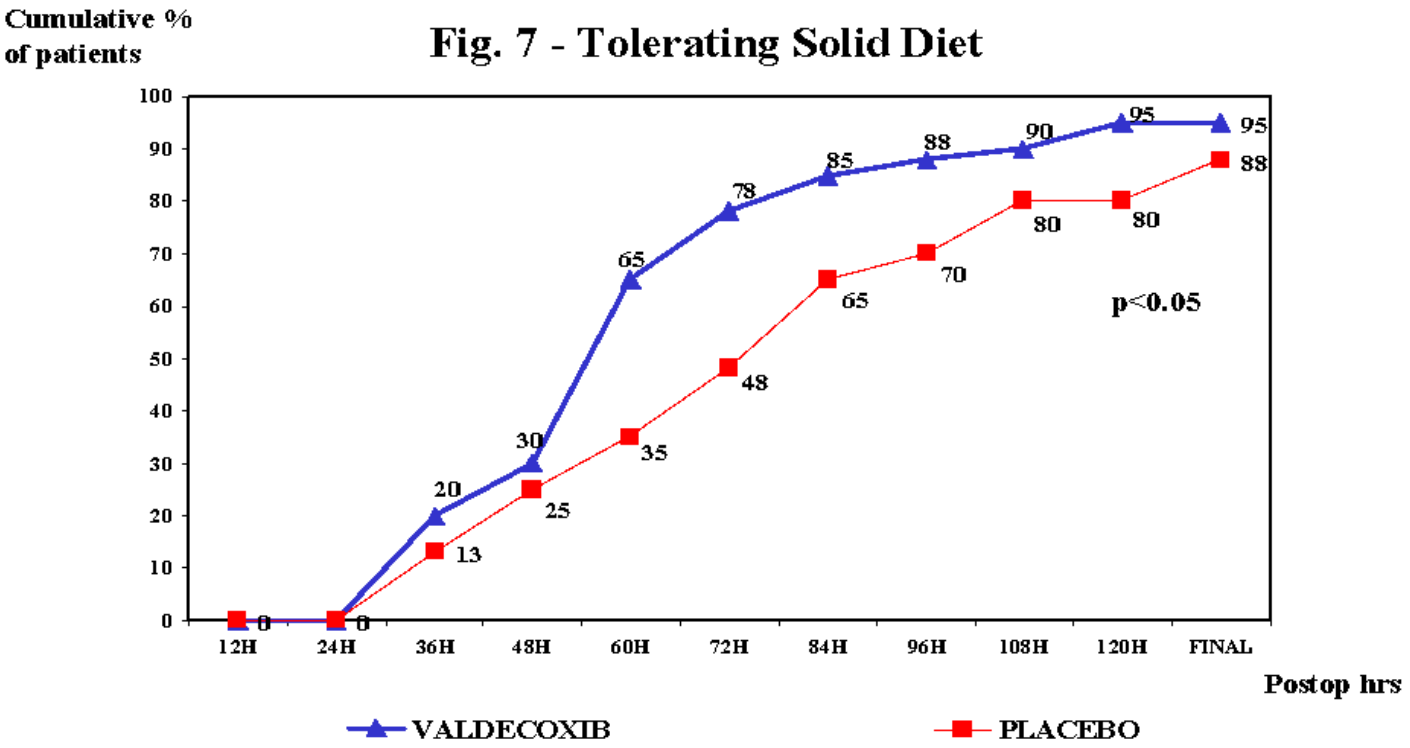
Fig. 5 – First Bowel Movement



Median 72h vs 84h



Median 24h vs 24h



Median 60h vs 72h

Fig. 8a - Pain Score - Zero

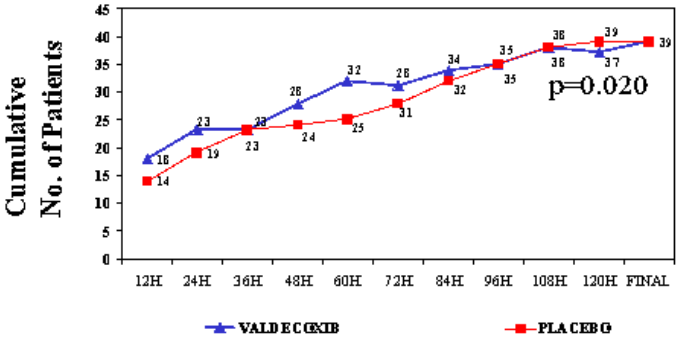


Fig. 8c - Nausea - None

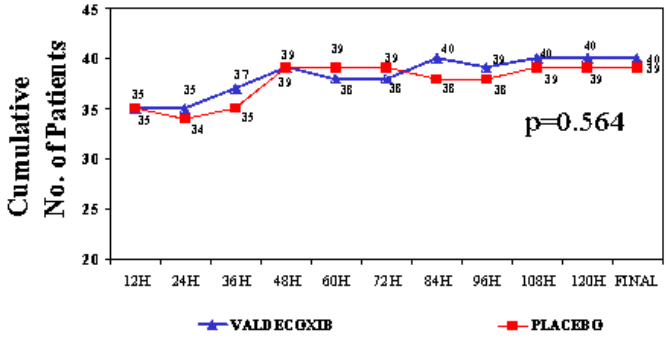
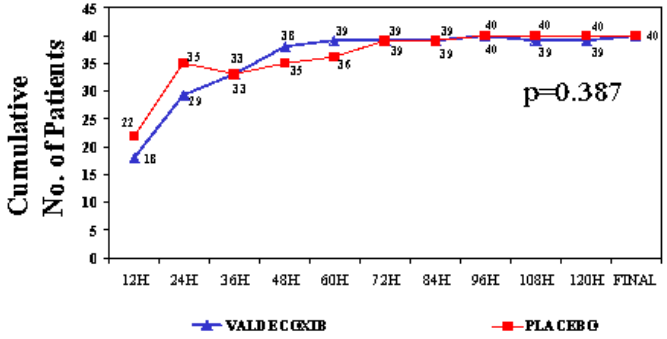


Fig. 8b - Sedation Score - Zero



Results

Placebo group - 3 had breakthrough pain that required intercostals nerve blocks and 1 patient had an AMI on POD 4.

Study group - 3 patients had breakthrough pain separately requiring intercostal nerve block, intramuscular pethidine and oral tramadol; 1 patient had an anastomotic dehiscence.

Patient characteristic	Study (n = 40)	Placebo (n = 39)	P
Length of Stay (days)			
Mean (SD)	4.9(2.7)	6.3(2.3)	0.009
Median	4.0	6.0	
Range	2 - 19	4 - 14	
Hospitalization Cost ($)			
Mean(SD)	11 210(14 510)	8 767(2 188)	0.447
Median	8 652	8 673	
Range	6 115 – 98 524	6 324 -15 025	

	Study (n = 6)	Placebo (n = 7)	P
Major morbidity (%)			
Acute myocardial infarct	0	1 (14.2)	0.317
Anastomotic dehiscence	1 (16.6)	0	
Pnuemonia	1 (16.6)	2 (28.5)	
Minor morbidity (%)			
Urinary tract infection	0	1 (14.2)	0.317
Wound related	2 (33.3)	1 (14.2)	
Prolonged ileus	0	2 (28.5)	
Thrombophlebitis	1 (16.6)	0	
Postoperation confusion	1 (16.6)	0	
Readmission within 30 days (%)	(n = 5)	(n = 3)	
Adhesion colic	1 (20.0)	2 (66.6)	0.317
Bleeding per rectum/stoma	2 (40.0)	1 (33.3)	
Stoma related	1 (20.0)	0	
Wound related	1 (20.0)	0	

Discussion

- Preemptive analgesia works in major abdominal bowel surgery
- Oral works, Parenteral not required
- Could not demonstrate the degree to which the preemptive administration of the COX-2 inhibitor contributed to the observed benefits of reduction of POI and opioid usage
- POI was also reduced probably as result of (1) reduced opioid usage, (2) early ambulation with better pain control and (3) attenuated inflammatory response
- Did not address the relative contribution of each factor toward the reduction of postoperative ileus though it is evident that all these factors can be attributed to COX-2 inhibtion

Asao T, Kuwano H, Nakamura J, et al. Gum chewing enhances early recovery from postoperative ileus after laparoscopic colectomy. J Am Coll Surg 2002 Jul; 195(1):30-2.

Le Blanc-Louvry I, Costaglioli B, Boulon C, et al. Does mechanical massage of the abdominal wall after colectomy reduce postoperative pain and shorten the duration of ileus? Results of a randomized study. J Gastrointest Surg 2002 Jan-Feb; 6(1):43-9.

Walch JM, Rabin BS, Day R, et al. The effect of sunlight on postoperative analgesic medication use: a prospective study of patients undergoing spinal surgery. Psychosom Med. 2005 Jan-Feb; 67(1): 156-63.

Conclusions

- Postoperative ileus is multifactorial in origin and hence a multimodal approach is likely to be the best means to enhance postoperative recovery.

- The addition of an oral COX-2-specific inhibitor pre- and postoperatively can reduce opioid use, postoperative ileus and length of stay when compared with a standard postoperative patient-controlled analgesia (PCA) morphine regimen after colorectal resection.