Mechanisms of reducing postoperative pain, nausea and vomiting: a systematic review of current techniques

Alex Rawlinson,[1] Nina Kitchingham,[2] Colin Hart,[3] Gregory McMahon,[3] Seok Ling Ong,[3] Achal Khanna[3]

10.1136/ebmed-2011-100265

[1]Department of Surgery, Northampton General Hospital, Northampton, UK
[2]Department of Anaesthesia, Leicester General Hospital, Leicester, UK
[3]Department of Surgery, Leicester Royal Infirmary, Leicester, UK

Correspondence to:
Achal Khanna
Dept of Surgery, Leicester Royal Infirmary Infirmary Square Leicester Le1 5ww, UK;
khannaachal@hotmail.com

Abstract

Background Multimodal recovery programmes decrease hospital stay. The objective of this systematic review was to assess how single-modality evidence-based care principles, regarding postoperative analgesia and postoperative nausea and vomiting (PONV) prophylaxis, combine to achieve this.

Methods A systematic review of randomised controlled trials was performed. Relevant trials compared postoperative epidural analgesia/parenteral opioid analgesia/paracetamol/non-steroidal anti-inflammatory drugs (NSAIDs) and postoperative antiemetics. The effect on recovery was evaluated in terms of length of hospital stay, pain intensity, duration of gastrointestinal dysfunction and incidence of PONV.

Results Twenty-three trials were included. Epidural anaesthesia failed to reduce length of stay or the incidence of PONV when compared to controls. Pain intensity and time to first bowel movement were reduced ($p<0.05$). Paracetamol did not reduce the incidence of PONV. NSAIDs reduced postoperative opioid consumption and the incidence of PONV ($p<0.05$). Dexamethasone and 5-HT3 antagonists reduced the incidence of PONV compared to controls.

Conclusions Epidural anaesthesia appears to not reduce length of hospital stay or incidence of PONV despite reducing pain intensity and ileus. NSAIDs are more effective than paracetamol in reducing postoperative opioid consumption and PONV, while dexamethasone and 5-HT3 antagonists are both effective in reducing PONV.

Introduction

Recent studies have demonstrated that the combination of single-modality evidence-based care principles into a multimodal effort enhances postoperative recovery leading to improvements in patient outcome.[1] The enhanced recovery after surgery (ERAS) group recommendations[2] integrated a range of perioperative interventions in order to improve postoperative recovery and enhance hospital discharge. These recommendations included a tailored anaesthetic using thoracic epidural catheters followed by non-opioid analgesics after the epidural is removed. Effective management of postoperative pain improves clinical outcome.[3] Persistent postoperative gastrointestinal dysfunction prolongs inpatient length of stay (LOS).[4] Recognition of the complications associated with poor postoperative pain control[5] has resulted in a greater awareness and subsequent improvement in management.

Systemic opioid administration, previously the mainstay of postoperative analgesia, delays the restoration of gastrointestinal function and can impede discharge.[6] The administration of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) in conjunction is designed to reduce side-effect profiles of opioid analgesics (OA) following the removal of the epidural.[7 8] Combination analgesia is effective and allows a reduction in dosage, further minimising opioid-related side effects.

Postoperative nausea and vomiting (PONV) has been identified as an essential component in achieving patient satisfaction[9] and can be more distressing than pain.[10 11] Untreated, one third of patients who undergo surgery will experience PONV, which is associated with prolonged stays in recovery, wound dehiscences and pulmonary complications.[12] PONV assessment allows appropriate antiemetic administration. A previous history of PONV, female gender, non-smoking and postoperative opioid administration are the most important predictors of developing PONV.[13]

This review will assess the evidence for individual treatments for postoperative pain, nausea and vomiting and whether they reduce hospital LOS, pain scores and gastrointestinal dysfunction. Questions to be addressed include whether the use of midthoracic epidural analgesia compared to intravenous opioids is effective in reducing length of hospital stay, postoperative pain scores and preventing gastrointestinal dysfunction and whether treatments reduce postoperative pain, nausea and vomiting. This review is primarily focused on outcomes in colorectal surgery, however studies from a range of surgical disciplines have been included in order to maximise the available evidence for review.

Methods

The National Library of Medicine's PubMed database, the Cochrane Register and Embase were all searched for relevant studies between January 1995 and August 2011. The medical subject heading (MeSH) terms used to review the literature were 'colon', 'sigmoid', 'rectal', 'abdominal surgery', 'orthopaedic surgery', 'urological surgery', 'obstetrics', 'gynaecology', 'ear', 'nose', 'throat', 'epidural,' 'analgesia,' 'nausea' and 'vomiting.' Additional studies were identified from hand searches of the bibliographies of selected publications as per PRISMA guidelines.

Inclusion criteria

Studies that were deemed of suitable design for inclusion were randomised (RCT) or clinical controlled trial in adults undergoing elective surgery. Studies that were included compared epidural analgesia with local anaesthetic versus parenteral opioid/non-OA. Studies assessing opioid consumption following paracetamol, NSAIDs or placebo administration and those that compared strategies to prevent PONV were also included.

Outcomes

Postoperative epidural analgesia and parenteral opioid administration were assessed in terms of 'LOS' as a

primary outcome measure. Secondary outcome measures included visual analogue pain scores (VAS), time taken to recover bowel function and incidence of PONV.

The effectiveness of paracetamol and NSAIDs were assessed by the additional requirement of opioid administration in the first 24 h after surgery. Secondary opioid-related outcomes included incidence of nausea and vomiting. The incidence of PONV in the first 24 h was also assessed following general anaesthetic (GA).

Results

Identification of trials

Twenty relevant articles were identified that compared epidural anaesthesia and OA. Five literature reviews were excluded, three were 'letters to the Editor', two were prospective studies lacking controls and two retrospective studies were all excluded. Eight randomised controlled trials subsequently remained and were analysed.

Nineteen studies were identified that assessed paracetamol/NSAID and opioid consumption. Six literature reviews were excluded. Three prospective studies lacked controls and one retrospective study were also excluded. Seventeen relevant publications evaluating PONV were identified. Six narrative reviews, three letters, two retrospective studies and two prospective studies lacking controls were also excluded. The remaining trials were of satisfactory design to merit inclusion for analysis.

Postoperative data was compared using the χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables in all included studies with the exception of the study by Sun *et al*,[14] which use Fisher's exact test for categorical data and Tukey's multicomparison test for continuous data.

Analysis of LOS, VAS and recovery of bowel function in epidural analgesia versus parenteral OA after surgery

Of the RCTs analysed, comparing epidural analgesia (EA) with local anaesthetic and parenteral OA, seven of the studies used thoracic bupivacaine and fentanyl[15–21] and one study used thoracic ropivacaine and fentanyl.[22] Established perioperative recovery programmes were frequently used and were based on multimodal analgesia (NSAIDs and paracetamol), PONV prophylaxis and early mobilisation. There was no statistically significant difference in LOS data between the epidural analgesia and control group (CG) (table 1) in any trial. Pain was assessed by the VAS at 24 h in seven studies,[15 17–22] 48 h in six studies[15 17 18 20–22] and at 72 h in six studies.[15 17–19 21 22] Epidurals reduced VAS to a greater degree than systemic opioid administration ($p<0.05$) in all of the studies. Six studies[15–17 20–22] examined the time to first bowel movement. Four demonstrated a significant reduction in the epidural group[15 17 20 22] ($p<0.05$). The incidence of PONV was recorded in five studies.[15 17 19 21 22] None of the studies established a significant difference between groups ($p<0.05$).

Analysis of opioid reduction with paracetamol and NSAID administration

Nine trials were included (tables 2 and 3). Three studies used paracetamol or propacetamol, five used NSAIDs (three types) and one study compared propacetamol and an NSAID.[23] One study assessed the efficacy of two types of NSAIDs.[24] All trials were placebo controlled. In all trials, patients received patient controlled analgesia (PCA) morphine for at least 24 h after surgery. A range of surgical procedures were included: orthopaedic (4 studies), gynaecological (1 study), obstetric (1 study), urological (one study) and general surgery (two studies).

Hernandez-Palazon *et al*[25] demonstrated a significant reduction ($p<0.05$) in morphine consumption in the paracetamol group compared to placebo. There was no reduction in the incidence of PONV in any paracetamol study. All of the RCT's that assessed NSAIDs revealed a significant reduction ($p<0.05$) in opioid consumption after major surgery (table 3).[23 24 26–29] A statistically significant reduction in the incidence of PONV was observed in three[24 26 29] out of the four trials in which it was measured.

Analysis of treatments preventing PONV

Six trials were included, all of which were placebo controlled (tables 4 and 5). A prospective factorial trial of six interventions[12]preventing PONV included all of the interventions recommended by the ERAS protocol. These included total intravenous anaesthesia (TIVA) and the administration of intravenous dexamethasone and ondansetron. Two RCT's assessed the efficacy of TIVA in

Table 1 RCTs of EA and local anaesthetic versus parenteral OA after colorectal surgery. LOS and visual analogue pain scores (/millimetres) expressed as mean values. A p Value ‹0.05 indicates statistical significance

			Number of patients		LOS (days)			VAS score (24 h)		VAS score (48 h)		VAS score (72 h)		
Author	Design	Year	OA	EA	OA	EA	p Value	OA	EA	OA	EA	OA	EA	p Value
Mann[15]	RCT	2000	26	20	11.90	11.90	›0.05	18	7	12	3	13	11	‹0.05
Paulsen[16]	RCT	2001	21	23	5.90	6.10	›0.05	39	18	42	17	39	9.5	‹0.05
Carli[17]	RCT	2001	21	21	7.50	8.40	›0.05	40	10	46	8	20	7	‹0.05
Carli[18]	RCT	2002	32	32	9.16	8.00	›0.05	34	12	33	11	22	13	‹0.05
Steinberg[22]	RCT	2003	21	20	6.20	6.46	›0.05	31	4	22	6	12	6	‹0.005
Rimaitis[19]	RCT	2003	50	50	10.00	11.00	›0.05	35	13	30	11	26	6	‹0.05
Zutshi[20]	RCT	2005	28	31	5.00	5.00	›0.05	31	25	33	25			‹0.05
Levy[21]	RCT	2011	30	29	2.80	3.70	›0.05	6.0	4.0	4.0	4.0	3.0	3.0	‹0.05

EA, epidural analgesia; LOS, length of stay; OA, opioid analgesia; RCT, randomised controlled trial; VAS,visual analogue pain scores.

Table 2 RCTs assessing paracetamol and it's effect on opioid consumption after major surgery. Comparison of analgesia regimens in CG and PG. In all studies, both groups were given an additional morphine patient controlled analgesia. Morphine consumption is described as mean values

			Number of patients			Analgesia regimens		Cumulative dose of morphine/mg
Author	Design	Year	CG	PG	Type of surgery	CG	PG	CG vs PG
Hernandez[25]	RCT	2001	21	21	Spinal fusion	Intravenous placebo (saline)	Intravenous propacetamol 2 g	112.2 vs 60.3
						Four times a day 72-h duration	Four times a day 72-h duration	(72 h postop)
Siddik[23]	RCT	2001	20	20	Caesarean section	Intravenous placebo	Intravenous propacetamol 2 g	66.7 vs 61.1
						Four times a day 24-h duration	Four times a day 24-h duration	(24 h postop)
Mimoz[45]	RCT	2001	38	38	Liver resection	Intravenous placebo (saline)	Intravenous propacetamol 2 g	43.0 vs 35.0
						Four times a day 24-h duration	Four times a day 24-h duration	(24 h postop)
Kvalsvik[46]	RCT	2003	30	30	Hysterectomy	PR placebo	PR paracetamol 1 g	99.6 vs 83.3
						Four times a day 60-h duration	Four times a day 60-h duration	(60-h postop)

CG, control groups; PG, paracetamol groups; RCT, randomised controlled trial.

Table 3 RCTs comparing NSAIDs in reducing opioid consumption and postoperative nausea and vomiting after major surgery. Comparison of analgesia regimens in CG and NG). In all studies, both groups were given an additional morphine. Morphine consumption is described as mean values

			Number of patients			Analgesia regimens		Cumulative dose of morphine/mg
Author	Design	Year	CG	NG	Type of surgery	CG	NG	CG vs NG
Rao[26]	RCT	2000	19	21	General	Intravenous placebo	Intravenous Ketoprofen 100 mg	50 vs 32
						Twice daily 24-h duration	Twice daily 24-h duration	(24 h postop)
Aubrun[27]	RCT	2000	25	25	Spinal fusion	Intravenous paracetamol 1 g	Intravenous Ketoprofen 100 mg	38 vs 28
						Four times a day 24-h duration	Three times a day 24-h duration	(24 h postop)
						Intravenous palcebo	Intravenous paracetamol 1 g	
						Three times a day 24-h duration	Four times a day 24-h duration	
Siddick[23]	RCT	2001	20	20	Caesarean section	Placebo	PR Diclofenac 100 mg	66.7 vs 36
							Three times a day 24-h duration	(24 h postop)
Chow[28]	RCT	2001	29	26	Urological	Intravenous placebo	Intravenous Ketorolac 30 mg	63 vs 39
						Four times a day 48-h duration	Four times a day 48-h duration	(48-h postop)
Alexander[24]	RCT	2002	13	23	Orthopaedic	Intravenous placebo	Intravenous Diclofenac 75 mg	51.6 vs 36.3
						Induction of GA	Induction of GA	(24 h postop)
Alexander[24]	RCT	2002	19	44	Orthopaedic	Intravenous placebo	Intravenous Ketorolac 60 mg	51.6 vs 47.2
						Induction of GA	Induction of GA	(24 h postop)
Hanna[29]	RCT	2003	30	57	Orthopaedic	Intramuscular placebo	Intramuscular Ketoprofen	65 vs 41
						Twice daily 24-h duration	Twice daily 24-h duration	(24 h postop)

CG, control groups; GA, general anaesthetic; NG, NSAID groups; NSAID, non-steroidal anti-inflammatory drugs; RCT, randomised controlled trial.

reducing the incidence of PONV.[12 30] Both studies demonstrated a statistically significant reduction in the incidence of PONV in the TIVA group compared to the traditional anaesthesia group. No significant reduction in PONV was observed at 48 or 72 h postoperatively.[30] Three RCTs[12 31 32] assessed the efficacy and timing of the administration of intravenous dexamethasone. All trials demonstrated a significant reduction in PONV with dexamethasone compared to placebo. In one trial,[31] dexamethasone administered at the start of surgery caused a significant reduction in the incidence of PONV in the immediate postoperative period (<2 h) compared to administration at the end of surgery. However, there were no statistically significant differences between the two groups at 24 h.

Four RCTs[12 14 33 34] assessed the efficacy and timing of 5-HT3 antagonist administration in preventing PONV. Three trials[12 33 34] demonstrated a significant improvement in PONV in the treatment group compared to placebo. In one trial,[12] the 5-HT3 antagonist was given at the end of surgery, while in the other two trials,[33 34] it was given at induction. Where a direct comparison of the timing of administration of 5-HT3 antagonists was made, no significant differences were found.

Discussion

This systematic review questions the role of epidural analgesia within the context of the ERAS protocol. Epidural analgesia does not shorten the duration of hospital stay or reduce the incidence of PONV after surgery. There is a significant reduction in the duration of ileus and VAS pain scores, however. Taguchi *et al*[35] demonstrated that the development of a postoperative ileus is a significant side effect following gastrointestinal surgery and delays recovery. Gastrointestinal dysfunction is also dependent upon anaesthetic and opioid administration.[36] Epidural catheter insertion may, however, be associated with inadequate pain management and technical failure. The appropriateness of their role in fast-track colonic surgery is open to debate.[20] Rigg *et al*[37] in their large RCT of epidural analgesia removed 40% of all epidural catheters inserted, either due to inadequate analgesia or malposition.

Multimodal analgesia, whereby morphine is administered with other non-OA, is used to reduce the cumulative morphine dose administered, and therefore morphine-related side effects, such as PONV.[38] This review demonstrates that postoperative NSAIDs are more effective than paracetamol when combined with PCA morphine and reduce opioid consumption and PONV, concurring with previous publications.[39] PCA morphine consumption is an indirect but useful approximation of the efficacy of other analgesics that have also been administered. Patients in CGs consumed, on average, 48 mg of morphine in the first 24 h. This amount was reduced by 35–40% with concurrent NSAID administration and by 15% by concurrent paracetamol consumption. The numbers of patients recruited in the trials assessed were comparatively small but the heterogeneity of the data sets precludes meta-analysis.

Combination use of paracetamol and NSAID is superior to paracetamol alone.[27] Paracetamol failed to reduce the incidence of PONV in any trial reviewed. The analgesic effect of paracetamol is proportional to the amount and rate of administration. It has been recommended that loading doses optimise effects.[40]

This systematic review demonstrates that NSAID administration reduces morphine requirements and results in a significant reduction in PONV.[23] But indiscriminate usage of NSAIDs, without due consideration to a patient's comorbidities, is ill advised due to the potential complications of bleeding and cardiac or renal dysfunction. The use of non-selective NSAIDs, such as diclofenac, has been shown to increase the risk of adverse cardiovascular events.[41] Non-selective NSAID use is also associated with adverse effects including a reduction in renal perfusion, thought to be secondary to reduced synthesis of vasodilatory prostaglandins such as PGE-2.[42] It has also been demonstrated that statistically significant increases occur in postoperative bleeding time.[43]

The evidence accrued from this review reveals that the use of epidural analgesia in colorectal surgery confers no benefit in reducing PONV. Apfel *et al*[12] demonstrated that

Table 4 RCTs comparing dexamethasone administration at induction or at the end of general anaesthesia as prophylaxis for PONV. (p value<0.05 indicates statistical significance). Dexamethasone (1) denotes administration at induction. Dexamethasone (2) denotes administration at the end of surgery

			Number of patients with nausea or vomiting			
			Dexamethasone (1)	Dexamethasone (2)	Placebo (3)	
Author	Type of surgery (no. of pts)	Hours postop	No. with PONV/total no. (%)			p Value
Apfel[12]	Superficial (595)	24 h	739/2596 (28.5)		992/2565 (38.7)	1:3<0.001
	Intra-abdominal (605)					
	ENT (465)					
	Gynaecology (2331)					
	Orthopaedic (764)					
	Laparoscopic (398)					
Wang[31]	Gynaecology (80)	2 h	6/40 (15)	18/40 (45)	21/40 (53)	1:2<0.01, 1:3<0.001
		24 h	10/40 (25)	11/40 (28)	22/40 (55)	1:2>0.05, 1:3<0.05
Feo[32]	Laparoscopic (101)	24 h	7/49 (14)		24/52 (46)	1:3<0.001

ENT, ear, nose and throat; PONV, postoperative nausea and vomiting; RCT, randomised controlled trial.

Table 5 Randomised controlled trials comparing the use and timing of serotonin receptor (5-HT3) antagonists in PONV prophylaxis (p<0.05 indicates a statistical significance). 5-HT3 antagonist (1) denotes administration at induction of anaesthesia. 5-HT3 Antagonist (2) denotes administration at the end of surgery

			Number of patients with nausea or vomiting			
			5-HT3 antagonist (1)	5-HT3 antagonist (2)	Placebo (3)	
Author	Type of surgery (no. of pts)	Hours postop	No. with PONV/total no. (%)			p Value
Apfel[12]	Superficial (595)	24 h		735/2576 (28.5)	996/2565 (38.5)	2:3 <0.001
	Intra-abdominal (605)					
	ENT (465)					
	Gynaecology (2331)					
	Orthopaedic (764)					
	Laparoscopic (398)					
Sun[14]	ENT (75)	24 h	22/25 (88)	16/25 (64)	23/25 (92)	1:3, 2:3>0.05
Liberman[33]	Laparoscopic (84)	12 h	19/42 (45)		35/42 (83)	1:3<0.05
Helmy[34]	Laparoscopic (80)	24 h	3/40 (7.5)		17/40 (42.5)	1:3<0.05

ENT, ear, nose and throat; PONV, postoperative nausea and vomiting.

PONV occurs in 59% of all patients undergoing GA with inhalational agents and nitrous oxide. The use of propofol reduces the risk of PONV by 19% and avoiding nitrous oxide by 12%. Combining propofol and air reduces the risk of PONV by 25%.[44]

Current ERAS recommendations advise the use of 5-hydroxytryptamine (5-HT3) receptor antagonists (ondansetron) and steroids (dexamethasone). These antiemetics are currently recommended for patients at moderate to severe risk of PONV. Ondansetron and dexamethasone are equally effective and each independently reduce the risk of PONV by 25%.[12] No statistically significant difference in the incidence of PONV was seen between the administration of 5-HT3 receptor antagonist at GA induction and the end of surgery.[14]

In conclusion, following surgery, epidural analgesia does not shorten the duration of hospital stay or reduce the incidence of PONV after surgery, though it may reduce the duration of ileus and pain scores. NSAIDs and paracetamol confer quantifiable morphine-sparing effects. NSAIDs provide a statistically significant reduction in morphine consumption and PONV. Combinations of non-OA act synergistically, have fewer complications and are more effective than a single non-opioid alone and for this reason, should be administered in the perioperative period.

Competing interests None.

References

1. **Chappell D**, Jacob M. Influence of non-ventilatory options on postoperative outcome. *Best Pract Res Clin Anaesthesiol* 2010;**24**:267–81.
2. **Lassen K**, Soop M, Nygren J, *et al*. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg* 2009;**144**:961–9.
3. **Wu CL**, Hurley RW, Anderson GF, *et al*. Effect of postoperative epidural analgesia on morbidity and mortality following surgery in medicare patients. *Reg Anesth Pain Med* 2004;**29**:525–33; discussion 515–19.
4. **Marret E**, Remy C, Bonnet F. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *Br J Surg* 2007;**94**:665–73.
5. **Perkins FM**, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 2000;**93**:1123–33.
6. **Cali RL**, Meade PG, Swanson MS, *et al*. Effect of morphine and incision length on bowel function after colectomy. *Dis Colon Rectum* 2000;**43**:163–8.
7. **Beaulieu P**. Non-opioid strategies for acute pain management. *Can J Anaesth* 2007;**54**:481–5.
8. Tan TY, Schug SA. Safety aspects of postoperative pain management. *Rev Analg* 2006;9:45–53.
9. **Eberhart LH**, Morin AM, Wulf H, *et al*. Patient preferences for immediate postoperative recovery. *Br J Anaesth* 2002;**89**:760–1.
10. **Gan T**, Sloan F, Dear Gde L, *et al*. How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesth Analg* 2001;**92**:393–400.
11. **van den Bosch JE**, Bonsel GJ, Moons KG, *et al*. Effect of postoperative experiences on willingness to pay to avoid postoperative pain, nausea, and vomiting. *Anesthesiology* 2006;**104**:1033–9.
12. **Apfel CC**, Korttila K, Abdalla M, *et al*. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004;**350**:2441–51.
13. **Apfel CC**, Läärä E, Koivuranta M, *et al*. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology* 1999;**91**:693–700.
14. **Sun R**, Klein KW, White PF. The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. *Anesth Analg* 1997;**84**:331–6.
15. **Mann C**, Pouzeratte Y, Boccara G, *et al*. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000;**92**:433–41.
16. **Paulsen EK**, Porter MG, Helmer SD, *et al*. Thoracic epidural versus patient-controlled analgesia in elective bowel resections. *Am J Surg* 2001;**182**:570–7.
17. **Carli F**, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. *Dis Colon Rectum* 2001;**44**:1083–9.
18. **Carli F**, Mayo N, Klubien K, *et al*. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. *Anesthesiology* 2002;**97**:540–9.
19. **Rimaitis K**, Marchertiene I, Pavalkis D. (Comparison of two different methods of analgesia. Postoperative course after colorectal cancer surgery). *Medicina (Kaunas)* 2003;**39**:129–37.

20. **Zutshi M**, Delaney CP, Senagore AJ, *et al*. Randomized controlled trial comparing the controlled rehabilitation with early ambulation and diet pathway versus the controlled rehabilitation with early ambulation and diet with preemptive epidural anesthesia/analgesia after laparotomy and intestinal resection. *Am J Surg* 2005;**189**:268–72.
21. **Levy BF**, Scott MJ, Fawcett W, *et al*. Randomized clinical trial of epidural, spinal or patient-controlled analgesia for patients undergoing laparoscopic colorectal surgery. *Br J Surg* 2011;**98**:1068–78.
22. **Steinberg RB**, Liu SS, Wu CL, *et al*. Comparison of ropivacaine-fentanyl patient-controlled epidural analgesia with morphine intravenous patient-controlled analgesia for perioperative analgesia and recovery after open colon surgery. *J Clin Anesth* 2002;**14**:571–7.
23. **Siddik SM**, Aouad MT, Jalbout MI, *et al*. Diclofenac and/or propacetamol for postoperative pain management after cesarean delivery in patients receiving patient controlled analgesia morphine. *Reg Anesth Pain Med* 2001;**26**:310–15.
24. **Alexander R**, El-Moalem HE, Gan TJ. Comparison of the morphine-sparing effects of diclofenac sodium and ketorolac tromethamine after major orthopedic surgery. *J Clin Anesth* 2002;**14**:187–92.
25. **Hernández-Palazón J**, Tortosa JA, Martínez-Lage JF, *et al*. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. *Anesth Analg* 2001;**92**:1473–6.
26. **Rao AS**, Cardosa M, Inbasegaran K. Morphine-sparing effect of ketoprofen after abdominal surgery. *Anaesth Intensive Care* 2000;**28**:22–6.
27. **Aubrun F**, Langeron O, Heitz D, *et al*. Randomised, placebo-controlled study of the postoperative analgesic effects of ketoprofen after spinal fusion surgery. *Acta Anaesthesiol Scand* 2000;**44**:934–9.
28. **Chow GK**, Fabrizio MD, Steer T, *et al*. Prospective double-blind study of effect of ketorolac administration after laparoscopic urologic surgery. *J Endourol* 2001;**15**:171–4.
29. **Hanna MH**, Elliott KM, Stuart-Taylor ME, *et al*. Comparative study of analgesic efficacy and morphine-sparing effect of intramuscular dexketoprofen trometamol with ketoprofen or placebo after major orthopaedic surgery. *Br J Clin Pharmacol* 2003;**55**:126–33.
30. **Visser K**, Hassink EA, Bonsel GJ, *et al*. Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide: postoperative nausea with vomiting and economic analysis. *Anesthesiology* 2001;**95**:616–26.
31. **Wang JJ**, Ho ST, Tzeng JI, *et al*. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. *Anesth Analg* 2000;**91**:136–9.
32. **Feo CV**, Sortini D, Ragazzi R, *et al*. Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. *Br J Surg* 2006;**93**:295–9.
33. **Liberman MA**, Howe S, Lane M. Ondansetron versus placebo for prophylaxis of nausea and vomiting in patients undergoing ambulatory laparoscopic cholecystectomy. *Am J Surg* 2000;**179**:60–2.
34. **Helmy SA**. Prophylactic anti-emetic efficacy of ondansetron in laparoscopic cholecystectomy under total intravenous anaesthesia. A randomised, double-blind comparison with droperidol, metoclopramide and placebo. *Anaesthesia* 1999;**54**:266–71.
35. TaguchiA, Sharma N, Saleem RM, *et al*. Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001;345:935–40.
36. **Person B**, Wexner SD. The management of postoperative ileus. *Curr Probl Surg* 2006;**43**:6–65.
37. **Rigg JR**, Jamrozik K, Myles PS, *et al*. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002;**359**:1276–82.
38. **Kehlet H**, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993;**77**:1048–56.
39. **Rømsing J**, Møiniche S, Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. *Br J Anaesth* 2002;**88**:215–26.
40. **Remy C**, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br J Anaesth* 2005;**94**:505–13.
41. **McGettigan P**, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;**296**:1633–44.
42. **Crilly MA**, Mangoni AA. Non-steroidal anti-inflammatory drug (NSAID) related inhibition of aldosterone glucuronidation and arterial dysfunction in patients with rheumatoid arthritis: a cross-sectional clinical study. *BMJ Open* 2011;**1**:e000076.
43. **Harley EH**, Dattolo RA. Ibuprofen for tonsillectomy pain in children: efficacy and complications. *Otolaryngol Head Neck Surg* 1998;**119**:492–6.
44. **Gan TJ**, Meyer TA, Apfel CC, *et al*. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2007;**105**:1615–28, table of contents.
45. **Mimoz O**, Incagnoli P, Josse C, *et al*. Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection. *Anaesthesia* 2001;**56**:520–5.
46. **Kvalsvik O**, Borchgrevink PC, Hagen L, *et al*. Randomized, double-blind, placebo-controlled study of the effect of rectal paracetamol on morphine consumption after abdominal hysterectomy. *Acta Anaesthesiol Scand* 2003;**47**:451–6.
47. **Tramèr MR**. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues. *Acta Anaesthesiol Scand* 2001;**45**:4–13.