

# Analgesic Treatment after Laparoscopic Cholecystectomy

## A Critical Assessment of the Evidence

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Acute pain after laparoscopic cholecystectomy is complex in nature. The pain pattern does not resemble pain after other laparoscopic procedures, suggesting that analgesic treatment might be procedure specific and multimodal. Randomized trials of analgesia after laparoscopic cholecystectomy were identified by systematic electronic literature searches (1985 to June 2005) supplemented with manual searching. The trials were categorized by well-defined criteria into high, moderate, or poor methodologic quality. Conclusions were based on trials of high and moderate methodologic quality. In total, 64 randomized analgesic trials were identified, comprising a total of 5,018 evaluated patients. The literature suggests a multimodal analgesic regimen consisting of a preoperative single dose of dexamethasone, incisional local anesthetics (at the beginning or at the end of surgery, depending on preference), and continuous treatment with nonsteroidal antiinflammatory drugs (or cyclooxygenase-2 inhibitors) during the first 3-4 days. Opioids should be used only when other analgesic techniques fail.

SEVERAL analgesic interventions with varying targets and mechanisms have been investigated for their influence on early pain after laparoscopic cholecystectomy. The current review was undertaken to analyze current literature to propose a procedure-specific, multimodal analgesic strategy after laparoscopic cholecystectomy.

There are numerous arguments for a procedure-specific assessment of the evidence of analgesic treatment after laparoscopic cholecystectomy. Postoperative pain is reduced compared with open traditional cholecystectomy,<sup>1</sup> but effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challenge.<sup>2</sup> In 17-41% of the patients, pain is the main reason for staying overnight in the hospital on the day of surgery,<sup>3-7</sup> and pain is the dominating complaint and the primary reason for prolonged convalescence after laparoscopic cholecystectomy.<sup>2,8</sup> Moreover, it has been hypothesized that intense acute pain after laparoscopic cholecystectomy may predict development of chronic

pain (e.g., postlaparoscopic cholecystectomy syndrome),<sup>9</sup> but this has not been studied prospectively.

The validity of postoperative quantitative estimates from non-procedure-specific analyses (number needed to treat) has recently been questioned because data are derived from a variety of procedures, which may potentially hinder the interpretation of the number needed to treat for specific procedures.<sup>10</sup> Therefore, it is proposed that analgesic data and optimized analgesic treatment should be specific for the type of surgical procedure.<sup>10-12</sup> In addition, growing evidence suggests that treatment of postoperative pain should be multimodal and opioid sparing to accelerate recovery and avoid potential side effects.<sup>13,14</sup>

The fact that acute pain after laparoscopic cholecystectomy is complex in nature and does not resemble pain after other laparoscopic procedures<sup>2,7,15</sup> suggests that effective analgesic treatment should be multimodal. Therefore, detailed prospective studies in individual laparoscopic procedures such as cholecystectomy, gynecologic procedures, hernia repair, and fundoplication have shown procedure-related individual pain patterns requiring procedure-specific analgesic treatment regimens.<sup>7,16</sup> In laparoscopic cholecystectomy, overall pain is a conglomerate of three different and clinically separate components: incisional pain (somatic pain), visceral pain (deep intraabdominal pain), and shoulder pain (presumably referred visceral pain).<sup>7</sup> Characteristically, overall pain after laparoscopic cholecystectomy carries a high interindividual variability in intensity and duration and is largely unpredictable.<sup>7</sup> Pain is most intense on the day of surgery and on the following day and subsequently declines to low levels within 3-4 days. However, pain may remain severe in approximately 13% of patients throughout the first week after laparoscopic cholecystectomy.<sup>7</sup> In this review, *pain* refers to postoperative pain not defined in detail unless stated otherwise.

In a recent systematic review of postoperative analgesia, the role of timing of treatment for postoperative pain relief was investigated (preemptive analgesia).<sup>17</sup> Based on findings from a variety of surgical procedures, the authors concluded preemptive and postoperative analgesic effects were comparable.<sup>17</sup> In the current review, timing of intervention refers to analgesic treatment at

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the start *versus* end of surgery. The issue is raised where data allows it and addressed in the sections relevant to each analgesic intervention.

## Methodologic Considerations

Clinical randomized trials of analgesia after laparoscopic cholecystectomy were included in the current review. Conclusions were restricted to findings from principal analgesic outcome trials. Trials were identified by literature searches in Medline, Embase, and the Cochrane Library (1985 to June 2005). The search string (free Text Terms and Medical Subject Headings [MeSH]) for pain consisted of *postoperative pain* and *laparoscopic cholecystectomy* in combination. Additional studies were identified by manually searching references provided by reviews and original articles. The searches were limited to English-language journals. The methodologic quality of the randomized trials was evaluated according to Slim *et al.*<sup>18</sup> A validated assessment form containing generic questions regarding research methodology in randomized trials was used. The assessment included 11 questions as to whether the trial had a stated aim, an adequate control group and statistics, an account of the selection process, randomization technique, adequate statistics, baseline equivalence, clearly defined study endpoint and unbiased assessment, description of the intervention procedure and operation, and adequate postoperative follow-up. Answers for each question were scored and trials were accordingly categorized into three quality groups: A = ideal quality, B = moderate quality, and C = poor quality. Randomized analgesic trials by the present author<sup>19</sup> were evaluated by an independent assessor (see acknowledgments).

## Results and Comments

In total, 64 randomized principal analgesic trials were identified, including a total of 5,018 evaluated patients (tables 1 and 2). Table 3 summarizes evidence-based grading of analgesic recommendations according to the criteria by the Oxford Center for Evidence based Medicine.<sup>†20</sup> In the following and for informative reasons, the pharmacologic mechanisms of the individual analgesics are briefly summarized, and the results from the randomized trials are listed and critically commented on.

### NSAIDs/COX-2 Inhibitors

The principal action of nonsteroidal antiinflammatory drugs (NSAIDs) (or cyclooxygenase-2 [COX-2] inhibitors) is modulation of the local inflammatory response by inhibiting cyclooxygenase in the spinal cord and periph-

ery to reduce prostanoid synthesis.<sup>21,22</sup> The analgesic effects of acetaminophen are mediated in the central nervous system by inhibiting the synthesis of prostaglandins.<sup>23</sup>

Optimally, analgesic therapy should be started in time to be effective at the time of emergence from anesthesia. Laparoscopic cholecystectomy is a short surgical procedure, often less than 1 h. It seems that initiation of treatment of NSAIDs or COX-2 inhibitors and the centrally acting acetaminophen shortly before or during laparoscopic cholecystectomy is optimal.<sup>24-26</sup> The analgesic effects of timing have been studied in one high-quality trial demonstrating that preoperative administered intravenous ketoprofen (100 mg) improved postoperative analgesia compared with postoperative administration<sup>24</sup> (table 2). Preoperative ketoprofen was shown to significantly improve postoperative analgesia compared with preoperative and postoperative propacetamol.<sup>24</sup> Another trial of poor methodologic quality found no analgesic advantage of early treatment *versus* late treatment with NSAIDs.<sup>27</sup> Data from other minor surgical procedures, such as breast biopsy,<sup>28,29</sup> have demonstrated that intravenous tenoxicam (20 mg) administered 30 min before surgery improved postoperative analgesia compared with treatment initiated at induction of anesthesia.

The analgesic efficacy of NSAIDs/COX-2 inhibitors and acetaminophen has been established in 10 trials after laparoscopic cholecystectomy (table 2). In many different surgical procedures, including laparoscopic cholecystectomy (table 2), the optimal benefit of NSAIDs or COX-2 inhibitors and acetaminophen is obtained by continuous prophylactic use by daily oral administration throughout the postdischarge period.<sup>26,27,30-37</sup> Evidence from other minor surgical procedures supports clinically relevant analgesic effects in laparoscopic cholecystectomy of acetaminophen alone and with additive effects when used in combination with other NSAIDs.<sup>38-40</sup> Acetaminophen has not been compared with placebo after laparoscopic cholecystectomy. The opioid sparing effects of NSAIDs or COX-2 inhibitors and acetaminophen are in the range of 20-30%.<sup>25-27,32,33,35,37,41</sup> Recent data from routine use of NSAIDs or COX-2 inhibitors and acetaminophen suggested hastened and higher quality of recovery along with less use of opioids in cholecystectomy and other minor surgical procedures.<sup>13,25,26,41,42</sup> Therefore, in laparoscopic cholecystectomy, a single intravenous dose of 40 mg parecoxib (30 min before operation) and 40 mg oral valdecoxib once daily on postoperative days 1-4 reduced pain intensity and opioid requirements.<sup>26</sup> Duration of stay in the postoperative anesthetic care unit and vomiting in the first 24 h were also significantly reduced, and patients slept better the first night, returned to normal activity earlier, and expressed greater satisfaction with the analgesic treatment compared with placebo treat-

† <http://cebm.jr2.ox.ac.uk> Accessed August 13, 2005.

**Table 1. Randomized Trials on the Analgesic Effects of Local Anesthetics after Laparoscopic Cholecystectomy**

Local Anesthetics	Author, Year	No. of Patients/Arms	LA (mg) in Saline (ml)	Instillation Sites	Timing	Effect on:					Study Quality
						Incisional Pain	Visceral Pain	Shoulder Pain	Pain (Not Defined)*	Opioid Needs	
Incisional LA (vs. placebo)	Sarac, <sup>46</sup> 1996	70/3	70 mg in 14 ml	B	Start vs. end	—	—	—	\$	\$	C
	Alexander, <sup>109</sup> 1996	80/2	100 mg in 40 ml	C vs. B	Start	—	—	—	\$		B
	Dath, <sup>110</sup> 1999	97/2	100 mg in 20 ml	D	End	—	—	—	\$		B
	Uzunköy, <sup>48</sup> 2000	45/3	75 mg in 30 ml	A, B, C	Start vs. end	—	—	—	\$	—	C
	Hasaniya, <sup>111</sup> 2001	84/2	100 mg in 20 ml	D	Start	\$	—	—	—	\$	C
	Papaziogas, <sup>45</sup> 2001	55/3	200 mg (ropivacaine) in 20 ml	D	Start	—	—	—	\$	\$	C
	Lepner, <sup>112</sup> 2003	80/4	100 mg in 80 ml	A, B, C	End	—	—		\$	\$	B
	Ure, <sup>47</sup> 1993	50/2	160 mg in 32 ml	A, B, C	Start	—	—	—			C
Intraperitoneal LA (vs. placebo)	Chundrigar, <sup>113</sup> 1993	58/2	50 mg in 20 ml	E	End		—		\$		C
	Pasqualucci, <sup>114</sup> 1994	37/3	200 mg in 40 ml	E, F, G	Start and end vs. end	—	—	—	\$	—	B
	Berven, <sup>115</sup> 1995	46/2	150 mg in 30 ml	F	End	—	—	—	—	\$	C
	Pasqualucci, <sup>50</sup> 1996	109/4	100 mg in 20 ml	E, F, G	Start vs. end	—	—	—	\$	—	C
	Szem, <sup>116</sup> 1996	55/2	100 mg in 100 ml	F, E, G	Start	—	—		\$		C
	Mraovic, <sup>117</sup> 1997	80/2	150 mg in 30 ml	E, F, G	Start	—	—	—	\$	—	C
	Weber, <sup>118</sup> 1997	150/3	50 mg in 10 ml	F	End	—	—	—	\$	\$	C
	Cuniffe, <sup>119</sup> 1998	63/2	50 mg in 500 ml	F	End	—	—	\$	—	\$	C
	Gharaibeh, <sup>120</sup> 2000	75/2	25 mg in 10 ml	E	After	—	—	\$	—	—	C
	Elhakim†, <sup>121</sup> 2000	50/2	200 mg (lidocaine) in 200 ml	F	End	—	—	\$	\$	\$	C
	Gupta, <sup>122</sup> 2002	39/2	100 mg in 20 ml	E	End		\$		—		A
	Maestroni, <sup>123</sup> 2002	60/2	380 mg (ropivacaine) in 200 ml	H	Start	—	—	—	\$		C
	Labaille, <sup>124</sup> 2002	37/3	100 mg/300 mg in 40 ml	E, F, I	Start		\$		—	\$	B
	Paulson, <sup>51</sup> 2003	66/4	150 mg in 30 ml	G, F, H	Start and end	—	—	—	\$	—	B
	Ng, <sup>125</sup> 2004	43/2	75 mg (levobupivacaine) in 30 ml	E, F	End	—	\$#		—		B
	Rademaker, <sup>126</sup> 1994	45/3	50 mg in 20 ml	F	End	—	—	—			C
	Jorist†, <sup>127</sup> 1995	40/2	100 mg in 80 ml	F	End						C
	Scheinin, <sup>128</sup> 1995	60/3	150 mg in 100 ml	F	End	—	—	—			C
	Raetzell, <sup>129</sup> 1995	30/3	125 mg in 50 ml	E, F	End	—	—	—			C
	Steinberg, <sup>130</sup> 1995	110/6	50 mg in 20 ml	E, F	End						A
	Busley, <sup>131</sup> 1999	33/2	25 mg + 100 mg (pilocaine) in 20 ml	F	End	—	—			—	C

(continued)

Table 1. (Continued)

Local Anesthetics	Author, Year	No. of Patients/Arms	LA (mg) in Saline (ml)	Instillation Sites	Timing	Effect on:					Study Quality
						Incisional Pain	Visceral Pain	Shoulder Pain	Pain (Not Defined)*	Opioid Needs	
Incisional and intraperitoneal LA (vs. placebo)	Elfberg, <sup>132</sup> 2000	65/2	2 mg/kg (no details)	E	End	—	—	—		—	C
	Zmora, <sup>133</sup> 2000	60/2	100 mg in 50 ml	E, F	End	—	—	—			C
	Jiranantararat, <sup>134</sup> 2002	80/2	100 mg in 20 ml	E, F, G	End	—	—	—			C
Incisional LA (vs. intraperitoneal LA)	Bisgaard†, 1999	58/2	286 mg (ropivacaine) in 66 ml	A, C, E, F, G	During	§			§	§	A
	Lee, <sup>44</sup> 2001	148/7	150 mg in 60 ml	C, E, F, G	End and start	§			—		A
	Johnson, <sup>52</sup> 1999	58/2	50 mg in 20 ml	E vs. C	End	—	—	—		—	C

Randomized controlled trials investigating the analgesic effects of incisional and intraperitoneal local anesthetics (LAs) after laparoscopic cholecystectomy. In all trials, postoperative pain was the primary outcome measure. LA is bupivacaine unless stated otherwise. Methodologic study quality was assessed as A = ideal, B = moderate, and C = poor (for details, see text).

\* The authors did not define postoperative pain (pain was registered on a visual analog scale and/or on a verbal rating scale). † Abdominal pain (not defined by the authors) was less than with placebo. ‡ Overall pain (defined in the text) was registered. § Significant effects in the treatment group. || Not significantly different from placebo. # Intraabdominal pain during inspiration was significantly reduced (pain at rest was not significantly reduced).

— = opioids were not allowed; A = periportal and intradermally; B = periportal and subcutaneously; C = periportal fascia, muscle and parietal peritoneum layer; D = periportal infiltration (not specified); E = region of gallbladder bed; F = hepatodiaphragmatic space; G = region of hepatoduodenal ligament; H = intraabdominal space (not defined by the authors); I = region between liver and kidney; end = instillation of LA at the end of surgery; start = instillation of LA at the start of surgery.

ment.<sup>26,32</sup> There were no differences in side effects or complications between treatment groups.

In summary, NSAIDs or COX-2 inhibitors are recommended for routine use in patients undergoing laparoscopic cholecystectomy (table 3). Treatment should be initiated shortly before or at induction of anesthesia or during surgery and continued for 3–4 days. The literature does not allow definite conclusions on drug dose.

### Local Anesthetics

Local anesthetics prevent transmission of nerve signals from the trauma site to the spinal cord and reduce neurogenic local inflammation at the trauma site.<sup>43</sup>

**Incisional Instillation.** Seven of eight trials favored the use of incisional local anesthetics (table 1). The methodologic quality of the trials was moderate or low. In half of the eight studies, incisional local anesthetics had significant opioid-sparing effects. A quantitative systematic analysis of postoperative visual analog scale pain scores from selected trials‡ found significant analgesia within 0–6 h,<sup>19,44–47</sup> 6–12 h,<sup>45</sup> and even 12–24 after laparoscopic cholecystectomy compared with con-

trols.<sup>44,45,48</sup> These investigations used various doses and application sites, and the study quality was questionable. Conclusions on exact analgesic duration are difficult, but median analgesic duration is at least 2–3 h after the end of surgery.<sup>19</sup> Two trials of poor methodologic quality investigated the effect of preemptive analgesic treatment<sup>46,48</sup> but failed to show advantages of local anesthetics administered before incision *versus* at the end of surgery.

**Intraperitoneal Instillation.** The analgesic effects of intraperitoneal local anesthetic blockade after laparoscopic cholecystectomy *versus* placebo have been investigated in 24 randomized trials (predominantly of poor or modest methodologic quality) (table 1). Nine trials were negative (1 high- and 8 poor-quality trials), and 15 trials demonstrated significant analgesic benefits (5 high- or moderate- and 10 poor-quality trials). There was no obvious relation between instillation site, dose, timing, and degree of pain relief (table 1). A recent combined systematic quantitative and qualitative review<sup>49</sup> (literature search 1966–1999) suggested a statistically significant weighted mean difference of 13 mm in visual analog scale scores in favor of intraperitoneal local anesthetic compared with placebo after laparoscopic cholecystectomy. However, a quantitative analysis of pooled data

‡ Procedure specific postoperative pain (PROSPECT). Available at: [www.postoppain.org](http://www.postoppain.org). June 1, 2003.

**Table 2. Randomized Trials on Various Analgesic Techniques after Laparoscopic Cholecystectomy**

Intervention	Author, Year	No. of Patients/ Arms	Effect on:		Study Quality
			Pain (Not Defined)*	Opioid Needs	
NSAIDs/COX-2 inhibitors					
NSAIDs (vs. placebo)	Liu, <sup>33</sup> 1993	60/2	†	†	B
	Wilson, <sup>34</sup> 1994	55/2	†	‡	C
	Fredman, <sup>35</sup> 1995	58/2	†	†	B
	Forse, <sup>36</sup> 1996	52/3	†	‡	B
	Lane, <sup>27</sup> 1996	68/3	†	†	C
	Munro, <sup>37</sup> 1998	37/2	‡	†	C
COX-2 inhibitors (vs. placebo)	Joshi and Gan, <sup>26,32</sup> 2004	263/2	†	†	A
	Horattas, <sup>25</sup> 2004	116/2	—	†	C
Preop ketoprofen (vs. postop ketoprofen or vs. preop and postop propacetamol)	Boccaro, <sup>24</sup> 2004	98/4	†	†	A
NSAIDs (vs. acetaminophen)	Owen, <sup>135</sup> 1997	90/2	‡	‡	C
Opioids					
Meperidine (vs. placebo)	Lane, <sup>27</sup> 1996	74/3	‡	†§	C
Intraperitoneal (vs. intramuscular pethidine)	O'Hanlon, <sup>136</sup> 2002	96/2	†	†§	A
Early (vs. late intraop morphine)	Munoz, <sup>137</sup> 2002	120/4	‡	†§	A
Morphine (vs. tramadol)	Naguib, <sup>138</sup> 1998	50/2	‡	‡	B
Tramadol (vs. placebo)	Naguib, <sup>55</sup> 2000	80/2	‡	‡	B
Controlled-release codeine (vs. acetaminophen plus codeine)	Chung, <sup>139</sup> 2004	69/2	‡	‡	B
Incisional morphine (vs. placebo or vs. bupivacaine)	Zajackowska, <sup>56</sup> 2004	150/5	‡	‡	B
Dexamethasone (vs. placebo)	Bisgaard, <sup>62</sup> 2003	80/2	†	†	A
Epidural analgesia (vs. control)	Luchetti, <sup>71</sup> 1996	40/2	†	—	C
	Fujii, <sup>72</sup> 1998	44/2	†	—	C
Intrathecal LA/morphine (vs. placebo)	Motamed, <sup>73</sup> 2000	32/2	†	†	B
Gabapentin (vs. placebo or tramadol)	Pandey, <sup>79</sup> 2004	459/3	†	†	B
Clonidine (vs. placebo)	Sung, <sup>81</sup> 2000	108/2	‡	†	C
	Laisalmi, <sup>82</sup> 2001	30/2	—	†	C
Preoperative NMDA receptor antagonists					
Dextromethorphan (vs. placebo)	Wu, <sup>87</sup> 1999	90/3	†	†	B
Dextromethorphan (vs. placebo and/or intravenous lidocaine)	Wu, <sup>89</sup> 2005	100/4	†	†	C
Dextromethorphan (vs. placebo and/or intravenous tenoxicam)	Yeh, <sup>88</sup> 2004	83/4	†	†	C
Ketamine (vs. placebo)	Mathisen, <sup>86</sup> 1999	60/3	‡	‡	B
Ketamine (vs. tramadol)	Launo, <sup>90</sup> 2004	40/2	‡	‡	C
Multimodal analgesia					
Opioids, ketorolac, and intraperitoneal/incisional local anesthetics (vs. placebo)	Michaloliakou, <sup>42</sup> 1996	45/2	†	†	B

Randomized controlled trials on the analgesic effects of various analgesic techniques in patients undergoing laparoscopic cholecystectomy. In all trials, postoperative pain was the primary outcome measure. Unless stated otherwise individual pain components were not studied. Methodologic study quality was assessed as A = ideal, B = moderate, and C = poor quality (for details, see text).

\* The authors did not define postoperative pain (pain was registered on a visual analog scale and/or verbal rating scale). † Significant effects in the treatment group. ‡ Not significantly different from placebo. § Additional opioid requirements are significantly reduced. || Overall pain, incisional pain, and visceral pain, but not shoulder pain, were significantly reduced in the dexamethasone group compared with placebo treatment (pain components are defined in the text).

— = not investigated; COX-2 = cyclooxygenase-2; intraop = intraoperative; NMDA = *N*-methyl-D-aspartate; NSAID = nonsteroidal antiinflammatory drug; postop = postoperative; preop = preoperative.

from these intraperitoneal local anesthetic trials is problematic. The intraperitoneal local anesthetic trials used highly variable study protocols with a variety of doses of

different local anesthetics ranging from 50 to 380 mg, and many different protocols were used for application sites of the local anesthetics (table 1). One trial of poor



**Table 3. Evidence-based Recommendations for Analgesic Treatment after Laparoscopic Cholecystectomy**

Analgesic Technique	Recommendations	Evidence (Strength)
NSAIDs/COX-2 inhibitors	Use of NSAIDs/COX-2 inhibitors is recommended. Treatment should start shortly before or during surgery. Optimal dose and timing are unknown. Duration of treatment should continue for 3–4 days after surgery (evidence IV (D)).	I (A)
	Use of acetaminophen in combination with NSAIDs/COX-2 inhibitors is recommended. Acetaminophen alone provides better analgesia than placebo treatment. Optimal dose and timing are unknown.	I (B)
Local anesthetics	Incisional local LA is recommended. Intraperitoneal LA may have a future role in postoperative analgesia, but results are conflicting and evidence from more trials of high quality is required. There is no conclusive information on dose and timing of LA infiltration.	I (A)
Opioids	Opioids provide effective treatment of postoperative intense pain. However, to accelerate recovery and avoid side effects, routine use of opioids is not recommended in patients after laparoscopic cholecystectomy. Postoperative short-acting opioids should be used when needed to supplement basic analgesic treatment.	I (B)
Steroids	Preoperative dexamethasone may have a future role in the treatment of pain after laparoscopic cholecystectomy, but more trials of high quality are required before recommended for routine use.	I (A)
Epidural analgesia (and intrathecal LA/morphine)	Epidural analgesia (and intrathecal LA/morphine) may be effective in laparoscopic cholecystectomy. However, because of potential risks and lack of rational cost–benefit ratio, routine use of this invasive technique cannot be recommended (evidence IV (D)).	I (B)
Gabapentin	Gabapentin may have a future role in the treatment of pain after laparoscopic cholecystectomy, but more trials of high quality are required before recommended for routine use.	I (B)
Clonidine	Current evidence does not support routine use.	IV (D)
NMDA receptor antagonists (dextromethorphan or ketamine)	Because of conflicting results from laparoscopic cholecystectomy and other surgical procedures, treatment with NMDA receptor antagonists cannot be recommended.	I (A and B)
Multimodal analgesic treatment	A combination of intravenous dexamethasone (8 mg) 90 min before operation, perioperative incisional LAs, NSAIDs/COX-2 inhibitors, and acetaminophen for 3–4 days may be useful. More data are needed to support this conclusion.	IV (C)

Evidence-based recommendations for prophylactic treatment of postoperative pain in patients undergoing laparoscopic cholecystectomy. Evidence is founded on trials of moderate and high methodologic quality with postoperative pain as the primary outcome. Categories of evidence<sup>20</sup>: I = based on at least one well-designed randomized controlled study, meta-analyses, or systematic reviews; II = based on at least one well-designed cohort or case-control studies; III = based on at least one uncontrolled study; IV = based on external consensus, opinions, or clinical experiences of respected authorities. Strength of recommendations: A = directly based on category I evidence; B = directly based on category II evidence or extrapolated recommendations from category I evidence; C = directly based on category III evidence or extrapolated recommendations from category II evidence; D = directly based category IV evidence or extrapolated recommendation from category I, II, or III evidence.

COX-2 = cyclooxygenase-2; LA = local anesthetic; LC = traditional laparoscopic cholecystectomy; NMDA = *N*-methyl-D-aspartate; NSAID = nonsteroidal antiinflammatory drug.

methodologic quality<sup>50</sup> suggested that early instillation of intraperitoneal local anesthetics provided better postoperative pain control compared with instillation at the end of surgery but was contradicted by another trial of moderate methodologic quality.<sup>51</sup>

**Incisional and Intraperitoneal Instillation.** Bisgaard *et al.*<sup>19</sup> applied a near-maximum dose of local anesthetic or placebo in a randomized trial (table 1). Ropivacaine (or saline) was infiltrated into the port incisions and ropivacaine (or saline) at several sites intraperitoneally (table 1). Both treatment groups were given NSAIDs and acetaminophen in fixed doses and opioids when needed. The local anesthetic regimen significantly reduced incisional pain during the first 3 h postoperatively.<sup>19</sup> No analgesic benefits on visceral pain or should

der pain were found, but overall pain was significantly reduced during the first 2 postoperative hours and opioid requirements were decreased during the first 3 postoperative hours. Nausea was significantly reduced in the ropivacaine group compared with placebo.<sup>19</sup> The findings were later replicated in a similar trial by Lee *et al.*<sup>44</sup> In a trial of low methodologic quality,<sup>52</sup> there were no analgesic differences between incisional *versus* intraperitoneal local anesthetic regimens (table 1).

In summary, the evidence from two high- and three moderate-quality trials supports routine use of local anesthetics in all trocar incisions to reduce pain after laparoscopic cholecystectomy (table 3). The literature does not provide conclusive information on specific dose and timing of local anesthetic infiltration, but a dose of more

than 100 mg bupivacaine (or other long-acting local anesthetics) is recommended. Routine use of intraperitoneal local anesthetics cannot be recommended, because of the low study quality in many trials and conflicting results.

### *Opioids*

Opioids reduce pain by decreasing local inflammation at the trauma site and in the dorsal horn by activating inhibitory pathways to the descending spinal segments.<sup>53,54</sup>

The analgesic effects of different treatment regimens of prophylactic opioids in laparoscopic cholecystectomy were investigated in seven randomized trials (table 2). The only positive trial in favor of prophylactic opioid treatment compared with placebo was of poor methodologic quality.<sup>55</sup> In a recent trial of moderate quality,<sup>56</sup> peripheral opioid analgesia was investigated. A low dose of opioid was injected at the trocar sites (2 mg morphine in 20 ml saline) alone or in a mixture with incisional bupivacaine. The authors found no significant analgesic differences compared with placebo treatment (table 2). One trial of high methodologic quality found that routine treatment of opioids at the beginning of operation conferred significantly better postoperative pain control than opioids given at the end of surgery.<sup>27</sup>

The valuable analgesic properties of opioids in the treatment of acute, intense postoperative pain after major and minor surgery are well accepted.<sup>57</sup> However, to hasten recovery and minimize opioid-related side effects (somnolence and sedation, nausea and vomiting, sleep disturbances, urinary retention, and respiratory depression), prophylactic use of opioids in postoperative pain is avoided.<sup>14,22,53,58</sup> Other drugs, such as NSAIDs or COX-2 inhibitors, incisional local anesthetics, and steroids have been shown to have valuable opioid-sparing effects (tables 1 and 2; see Multimodal Analgesia section).

In summary, there are no specific data to support prophylactic use of opioids in patients after laparoscopic cholecystectomy (table 3). Based on findings from a variety of surgical procedures, the use of short-acting opioids is the treatment of choice for intense persistent pain and to supplement other analgesics if no surgical reason is found as the cause of the pain after laparoscopic cholecystectomy.

### *Steroids*

The onset of biologic action is at 1–2 h and the timing of preoperative steroid administration seem to be important to attenuate postoperative inflammatory activation<sup>59</sup> but have not been specifically addressed in surgical patients. The analgesic effects of steroids are mainly provided through peripheral inhibition of phospholipase enzyme and hereby decreasing products of cyclooxygen-

ase and lipoxygenase pathways in the inflammatory response.<sup>59,60</sup>

A recent review based on available randomized trials (1966 to May 2001) focused on the effects of perioperative single-dose steroid administration.<sup>61</sup> The authors concluded that steroids may have analgesic effects in minor surgical procedures such as hemorrhoidectomy, hallux valgus correction, thyroidectomy, and dental surgery.<sup>61</sup> A recent randomized trial investigated analgesia using a single dose of dexamethasone (8 mg) intravenously given 90 min before laparoscopic cholecystectomy (table 2).<sup>62</sup> Postoperative pain and supplementary opioid requirements were reduced by approximately 50% in the dexamethasone group compared with placebo. Patients in the dexamethasone group reported significantly lower levels of postoperative fatigue, nausea, and vomiting, and resumed normal activities faster compared with placebo.<sup>62</sup> However, other studies using a single intravenous dose of 8 mg<sup>63</sup> or 5 mg<sup>64</sup> or a varying dose of dexamethasone in combination with ondansetron<sup>65</sup> failed to show analgesic benefits after laparoscopic cholecystectomy. In these trials, dexamethasone was given immediately before incision, and postoperative nausea and vomiting were the principal outcomes. All trials in laparoscopic cholecystectomy<sup>62–65</sup> and in other surgical procedures<sup>66</sup> found significant antiemetic effects using prophylactic dexamethasone, and no side effects were observed. In the dexamethasone trials reporting no analgesic effects, postoperative pain was not the principal outcome, and dexamethasone was administered immediately before the operation.<sup>63–65</sup>

Obviously, concerns about a possible association between steroids and impaired wound healing, postoperative infection, or other complications are important. In a meta-analysis,<sup>67</sup> it was concluded that perioperative administration of high-dose methylprednisolone (30–35 mg/kg), a dose equivalent to 50 times the dose of dexamethasone (8 mg), was not associated with significant side effects. Also, a recent meta-analysis of postoperative nausea and vomiting indicated that a single dose of dexamethasone did not increase infectious or other complications.<sup>68</sup>

In summary, the analgesic potential of dexamethasone after laparoscopic cholecystectomy warrants further evaluation before final conclusions can be made (table 3).

### *Epidural Analgesia*

Epidural local anesthetics work by blocking afferent nerve activity at the spinal level.<sup>69</sup>

The efficacy of postoperative epidural analgesia in major surgical procedures is well established.<sup>70</sup> Poor methodologic quality in trials in laparoscopic cholecystectomy have suggested significant analgesic benefits of epidural analgesia<sup>71,72</sup> and intrathecal morphine/local anesthesia<sup>73</sup> compared with controls (table 2). However, it may be argued that safety, cost-benefit, and analgesic

superiority over noninvasive analgesic regimens must be documented before epidural analgesia is recommended for laparoscopic cholecystectomy in otherwise healthy patients. The effect of timing of analgesia has not been studied in laparoscopic cholecystectomy.

In summary, epidural analgesia and intrathecal local anesthesia/morphine probably provide effective control of pain after laparoscopic cholecystectomy. However, these invasive techniques cannot be recommended as routine in laparoscopic cholecystectomy, because of the potential risks (table 3).

### *Gabapentin*

Gabapentin, an antiepileptic drug, works centrally by reducing the release of monoamine neurotransmitters.<sup>74</sup> In patients undergoing breast surgery,<sup>75,76</sup> in patients undergoing spinal surgery,<sup>77</sup> and after abdominal hysterectomy,<sup>78</sup> gabapentin (1,200 mg) had clinically important effects on postoperative pain and morphine consumption. In a recent large-scale, double-blind, randomized trial of 459 patients undergoing laparoscopic cholecystectomy (moderate methodologic quality; table 2), the analgesic effects of a very low dose of 300 mg oral gabapentin 2 h before operation was compared with 100 mg oral tramadol or placebo.<sup>79</sup> Gabapentin significantly decreased total opioid consumption by 17% *versus* tramadol and by 37% *versus* placebo. Also, there was a significant decrease in visual analog scale pain scores compared with placebo and tramadol treatment.<sup>79</sup> The effect of timing of administration of gabapentin has not been studied in laparoscopic cholecystectomy.

In summary, dose-response studies of the analgesic efficacy of gabapentin are warranted in laparoscopic cholecystectomy before this treatment can be recommended as routine (table 3).

### *Clonidine*

Clonidine, an  $\alpha_2$  agonist, reduces peripheral sympathetic outflow, inhibits the release of substance P from the dorsal horn, and suppresses noxious activity at the spinal cord level.<sup>80</sup>

Two randomized trials<sup>81,82</sup> indicated clinically important postoperative analgesic effects using a single 150- $\mu$ g or 3- $\mu$ g/kg dose of clonidine before laparoscopic cholecystectomy. Unfortunately, both trials were of very poor methodologic quality, and conclusions about analgesia are not possible (tables 2 and 3). The effect of timing of administration of clonidine has not been studied in laparoscopic cholecystectomy.

In summary, current evidence does not support routine use (table 3).

### *NMDA Receptor Antagonists*

N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine and dextromethorphan) reduce spinal

nociceptive neuron activity, thereby changing spinal nociceptive processing and hyperexcitability.<sup>83</sup>

It remains unclear whether prophylactic treatment with NMDA receptor antagonists has a role in the control of pain after surgery.<sup>84,85</sup> In laparoscopic cholecystectomy, the analgesic effects of preemptive NMDA receptor antagonists have been investigated in five randomized trials of predominantly poor or moderate methodologic quality (table 2).<sup>86-90</sup> In the only trial of moderate methodologic quality and reporting positive findings, dextromethorphan (40 mg intramuscular) administered 30 min before incision provided significantly better postoperative pain relief than treatment after surgery and control groups.<sup>87-89</sup> In a trial of moderate quality, Mathisen *et al.*<sup>86</sup> found no significant analgesic effects of a racemic ketamine (1 mg/kg intravenous) treatment administered 3-10 min before surgical incision compared with ketamine treatment at skin closure or placebo treatment.

In summary, analgesic efficacy from future high-quality trials with NMDA receptor antagonists in laparoscopic cholecystectomy is essential before this treatment can be recommended (table 3).

### *Multimodal Analgesia*

Results from patients after outpatient hernia repair,<sup>91</sup> major upper gastrointestinal surgery,<sup>92,93</sup> cesarian delivery,<sup>94,95</sup> and abdominal hysterectomy<sup>96</sup> have suggested enhanced analgesic efficacy using multimodal analgesic strategies compared with unimodal analgesic treatment as assessed by pain, opioid needs, pulmonary dysfunction, physical activity, mood and sleep disturbances.<sup>96</sup>

The complexity of pain after laparoscopic cholecystectomy provides rationale for a multimodal analgesic approach. Michaloliakou *et al.*<sup>42</sup> investigated the effect of a multimodal analgesic therapy or placebo in a randomized trial in 45 patients undergoing laparoscopic cholecystectomy (table 2). The treatment group received a combination of preoperative intramuscular opioid, ketorolac, and combined incisional-intraperitoneal local anesthetic blockade. The multimodal analgesia almost eliminated reports of postoperative pain and need for supplemental morphine, and recovery, mobilization, and functional activity were significantly enhanced. Although not based on randomized comparison, it is noteworthy that 65-92% of patients receiving a single mode of analgesic treatment may need supplementary opioids on the day of laparoscopic cholecystectomy.<sup>7,32</sup> Only 20-29% of patients treated with a multimodal analgesic treatment require supplemental opioids.<sup>42,62</sup> However, in studies by Bisgaard *et al.*<sup>62,97</sup> using a prophylactic multimodal analgesia, pain was not eliminated after the operation. In these trials, the pain treatment consisted of intraoperative opioids, incisional local anesthetics, and NSAIDs in combination with dexamethasone.<sup>62</sup> The addition of gabapentin and/or clonidine and/or ketamine,



and/or NMDA receptor antagonists may have added additional analgesic control. Two trials in laparoscopic cholecystectomy suggested that preincisional dextromethorphan in combination with and tenoxicam<sup>88</sup> or intravenous lidocaine<sup>89</sup> provided additional pain relief compared with placebo. However, both trials were of poor methodologic quality, precluding definitive conclusions.

In summary, the complexity of pain after laparoscopic cholecystectomy and previous investigations using multimodal analgesic treatment in a variety of surgical procedures support that pain after laparoscopic cholecystectomy should be managed using a multifaceted opioid-sparing analgesic regimen (table 3). High-quality trials are needed in laparoscopic cholecystectomy to provide evidence for the optimal multimodal analgesic regimen.

#### *Miscellaneous*

Six randomized trials in laparoscopic cholecystectomy of various quality with different interventions (propofol-based general anesthesia *vs.* desflurane-based anesthesia,<sup>98,99</sup> metoclopramide [20 mg] *vs.* ondansetron,<sup>100</sup> preoperative carbohydrate beverage *vs.* placebo,<sup>101</sup> and outpatient *vs.* inpatient laparoscopic cholecystectomy)<sup>102</sup> monitored postoperative pain, but pain was by no means a principal outcome measure, and conclusions about analgesia are not possible.

#### *Interventions to Reduce Incisional, Visceral, and Shoulder Pain*

Few analgesic trials have investigated the different components of pain after laparoscopic cholecystectomy (tables 1 and 2). The literature suggests that incisional pain is reduced by incisional local anesthetics and dexamethasone (tables 1 and 2). Visceral pain is reduced by intraperitoneal local anesthetics and dexamethasone, although findings are not uniform (tables 1 and 2). There are no randomized analgesic trials of high or moderate methodologic quality to provide evidence for the treatment of shoulder pain (tables 1 and 2).

Two investigations from the surgical literature, both of moderate methodologic quality, found that carbon dioxide insufflation pressure of 7–9 mmHg compared with a high insufflation pressure (12–14 mmHg) reduced postoperative shoulder pain after laparoscopic cholecystectomy.<sup>103,104</sup> In patients with American Society of Anesthesiologists physical status of I or II, the hemodynamic and circulatory effects of a 12- to 14-mmHg pneumoperitoneum are generally not clinically relevant, but in patients with American Society of Anesthesiologists physical status of III or IV, the use of the lowest intra-abdominal pressure allowing adequate exposure is recommended.<sup>105</sup> Finally, two randomized surgical trials of high and moderate methodologic quality found significantly lower levels of incisional pain scores using a micro-

laparoscopic cholecystectomy technique (3.5-mm trocar instrument *vs.* 10- and 5-mm trocar instruments).<sup>97,106</sup>

In summary, only a small number of analgesic trials addressed individual pain components after laparoscopic cholecystectomy, and final conclusions are not possible.

#### **Future Directions**

The methodologic quality of randomized trials of pain after laparoscopic cholecystectomy is generally low and should be improved in future trials. The large interindividual variation in pain intensity after laparoscopic cholecystectomy should be taken into consideration in the statistical planning.<sup>7</sup>

The effects of multimodal analgesic therapy should be investigated against placebo in patients after laparoscopic cholecystectomy. The clinical implications of pain relief and opioid-sparing effects (quality of recovery, nausea and vomiting, general well-being, patient's satisfaction, sleep, dizziness, fatigue, and duration of convalescence) should be further assessed. The analgesic cost effectiveness of gabapentin, clonidine, ketamine, and NMDA receptor antagonists should be investigated in high-quality trials before being implemented.

Slow-release preparations of local anesthetics<sup>107,108</sup> with prolonged postoperative pain relief should be studied. Intraperitoneal instillation of local anesthetics is easy, safe, and inexpensive. Therefore, it is hoped that trials of high quality will be performed to provide definitive conclusions on the analgesic effect of intraperitoneal application of local anesthetics.

More information is needed about dose-response aspects of incisional local anesthetics and NSAIDs and COX-2 inhibitors.

The ability for a single-dose steroid therapy (8 mg dexamethasone) to improve analgesic treatment and other clinical outcomes (fatigue, nausea and vomiting, general well-being, etc.) should be tested in a large, multicenter trial of high methodologic quality. The analgesic efficacy of preoperative intravenous dexamethasone 1–2 h before *versus* immediately before surgery should be investigated. Self-administration of oral steroids 1–2 h before surgery could be investigated in a randomized trial.

Finally, the hypothesis that severe acute pain after laparoscopic cholecystectomy predicts development of chronic pain (such as post-laparoscopic cholecystectomy syndrome)<sup>9</sup> should be investigated in future well-defined, prospective, large-scale studies. Whether optimized perioperative analgesic treatment reduces risk of chronic pain after laparoscopic cholecystectomy is a question that needs to be answered.

## Conclusions

The complexity of pain after laparoscopic cholecystectomy suggests that effective treatment of postoperative pain should be multimodal. Based on a critical analysis of current literature, the regimen includes preoperative single dose of dexamethasone, incisional local anesthetics (at the beginning or at the end of operation, depending on preference), and regular use of NSAIDs or COX-2 inhibitors combined during the first 3–4 postoperative days, including the day of surgery. Prophylactic treatment of postoperative opioids is not recommended because of the many potential side effects. Short-acting opioids should be used only on demand when other analgesic techniques fail.

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