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 analytic trials were identified, comprising a total of 5,018 evaluted patients. The literature suggests a multimodal analgesic regimen consisting of a preoperative single dose of dexmethasone, 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, but effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challenge. In 17–41% of the patients, pain is the main reason for staying overnight in the hospital on the day of surgery, and pain is the dominating complaint and the primary reason for prolonged convalescence after laparoscopic cholecystectomy. Moreover, it has been hypothesized that intense acute pain after laparoscopic cholecystectomy may predict development of chronic pain (e.g., postlaparoscopic cholecystectomy syndrome), 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. Therefore, it is proposed that analgesic data and optimized analgesic treatment should be specific for the type of surgical procedure. In addition, growing evidence suggests that treatment of postoperative pain should be multimodal and opioid sparing to accelerate recovery and avoid potential side effects.

The fact that acute pain after laparoscopic cholecystectomy is complex in nature and does not resemble pain after other laparoscopic procedures suggests that effective analgesic treatment should be multimodal. Therefore, detailed prospective studies in individual laparoscopic procedures such cholecystectomy, gynecologic procedures, hernia repair, and fundoplication have shown procedure-related individual pain patterns requiring procedure-specific analgesic treatment regimens.

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). Characteristically, overall pain after laparoscopic cholecystectomy carries a high interindividual variability in intensity and duration and is largely unpredictable. 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. 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). Based on findings from a variety of surgical procedures, the authors concluded preemptive and postoperative analgesic effects were comparable. In the current review, timing of intervention refers to analgesic treatment at
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.18 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 author19 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.†20 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 periphery to reduce prostanoïd synthesis.21,22 The analgesic effects of acetaminophen are mediated in the central nervous system by inhibiting the synthesis of prostaglandins.23

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.24–26 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 administration24 (table 2). Preoperative ketoprofen was shown to significantly improve postoperative analgesia compared with preoperative and postoperative propacetamol.24 Another trial of poor methodologic quality found no analgesic advantage of early treatment versus late treatment with NSAIDs.27 Data from other minor surgical procedures, such as breast biopsy,28,29 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.26,27,30–37 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.38–40 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%.25–27,32,33,35,37,41 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.13,25,26,41,42 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.26 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-

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

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

(continued)
Incisional and intraperitoneal LA (vs. placebo)

<table>
<thead>
<tr>
<th>Local Anesthetics</th>
<th>Author, Year</th>
<th>No. of Patients/Arms</th>
<th>LA (mg) in Saline (ml)</th>
<th>Instillation Sites</th>
<th>Timing</th>
<th>Effect on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elberg,‡132</td>
<td>2000</td>
<td>65/2</td>
<td>2 mg/kg (no details)</td>
<td>E</td>
<td>End</td>
<td>— — — —</td>
</tr>
<tr>
<td>Zmora,‡133</td>
<td>2000</td>
<td>60/2</td>
<td>100 mg in 50 ml</td>
<td>E, F</td>
<td>End</td>
<td>— — — —</td>
</tr>
<tr>
<td>Jiranantarat,‡134</td>
<td>2000</td>
<td>80/2</td>
<td>100 mg in 20 ml</td>
<td>E, F, G</td>
<td>End</td>
<td>— — — —</td>
</tr>
</tbody>
</table>

Incisional LA (vs. intraperitoneal LA)

<table>
<thead>
<tr>
<th>Local Anesthetics</th>
<th>Author, Year</th>
<th>No. of Patients/Arms</th>
<th>LA (mg) in Saline (ml)</th>
<th>Instillation Sites</th>
<th>Timing</th>
<th>Effect on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisgaard‡,19</td>
<td>1999</td>
<td>58/2</td>
<td>286 mg (ropivacaine) in 66 ml</td>
<td>A, C, E, F, G</td>
<td>During</td>
<td>§</td>
</tr>
<tr>
<td>Lee,44 2001</td>
<td>148/7</td>
<td>150 mg in 60 ml</td>
<td>C, E, F, G</td>
<td>End and start</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>Johnson,52 1999</td>
<td>58/2</td>
<td>50 mg in 20 ml</td>
<td>E vs. C</td>
<td>End</td>
<td>— — — —</td>
<td>— — — —</td>
</tr>
</tbody>
</table>

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).

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.43

**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,19,44–47 6–12 h,45 and even 12–24 after laparoscopic cholecystectomy compared with controls.44,45,48 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.19 Two trials of poor methodologic quality investigated the effect of preemptive analgesic treatment46,48 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 review49 (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...
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>
<thead>
<tr>
<th>Intervention</th>
<th>Author, Year</th>
<th>No. of Patients/Arms</th>
<th>Effect on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs/COX-2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs (vs. placebo)</td>
<td>Liu,33 1993</td>
<td>60/2</td>
<td>†</td>
</tr>
<tr>
<td>Wilson,34 1994</td>
<td>55/2</td>
<td>†</td>
<td>†§</td>
</tr>
<tr>
<td>Fredman,35 1995</td>
<td>58/2</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Forse,36 1996</td>
<td>52/3</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Lane,27 1996</td>
<td>68/3</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Munro,37 1998</td>
<td>37/2</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>COX-2 inhibitors (vs. placebo)</td>
<td>Joshi and Gan,26,32 2004</td>
<td>263/2</td>
<td>†</td>
</tr>
<tr>
<td>Preop ketoprofen (vs. postop ketoprofen or vs. preop and postop propacetamol)</td>
<td>Horattas,28 2004</td>
<td>116/2</td>
<td>—</td>
</tr>
<tr>
<td>NSAIDs (vs. acetaminophen)</td>
<td>Boccara,24 2004</td>
<td>98/4</td>
<td>†</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine (vs. placebo)</td>
<td>Lane,27 1996</td>
<td>74/3</td>
<td>‡</td>
</tr>
<tr>
<td>Intraperitoneal (vs. intramuscular pethidine)</td>
<td>O’Hanlon,36 2002</td>
<td>96/2</td>
<td>†</td>
</tr>
<tr>
<td>Early (vs. late intraop morphine)</td>
<td>Munoz,37 2002</td>
<td>120/4</td>
<td>‡</td>
</tr>
<tr>
<td>Morphine (vs. tramadol)</td>
<td>Naguib,38 1998</td>
<td>50/2</td>
<td>‡</td>
</tr>
<tr>
<td>Tramadol (vs. placebo)</td>
<td>Naguib,55 2000</td>
<td>80/2</td>
<td>†</td>
</tr>
<tr>
<td>Controlled-release codeine (vs. acetaminophen plus codeine)</td>
<td>Chung,39 2004</td>
<td>69/2</td>
<td>‡</td>
</tr>
<tr>
<td>Incisional morphine (vs. placebo or vs. bupivacaine)</td>
<td>Zajaczkowska,56 2004</td>
<td>150/5</td>
<td>‡</td>
</tr>
<tr>
<td>Dexamethasone (vs. placebo)</td>
<td>Bisgaard,62 2003</td>
<td>80/2</td>
<td>‡</td>
</tr>
<tr>
<td>Epidural analgesia (vs. control)</td>
<td>Luchetti,71 1996</td>
<td>40/2</td>
<td>†</td>
</tr>
<tr>
<td>Intrathecal LA/morphine (vs. placebo)</td>
<td>Fujii,72 1998</td>
<td>44/2</td>
<td>†</td>
</tr>
<tr>
<td>Gabapentin (vs. placebo or tramadol)</td>
<td>Motamed,73 2000</td>
<td>32/2</td>
<td>†</td>
</tr>
<tr>
<td>Clonidine (vs. placebo)</td>
<td>Pandey,79 2004</td>
<td>459/3</td>
<td>†</td>
</tr>
<tr>
<td>Preoperative NMDA receptor antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan (vs. placebo)</td>
<td>Wu,67 1999</td>
<td>90/3</td>
<td>†</td>
</tr>
<tr>
<td>Dextromethorphan (vs. placebo and/or intravenous lidocaine)</td>
<td>Wu,69 2005</td>
<td>100/4</td>
<td>†</td>
</tr>
<tr>
<td>Dextromethorphan (vs. placebo and/or intravenous tenoxicam)</td>
<td>Yeh,88 2004</td>
<td>83/4</td>
<td>†</td>
</tr>
<tr>
<td>Ketamine (vs. placebo)</td>
<td>Mathisen,86 1999</td>
<td>60/3</td>
<td>‡</td>
</tr>
<tr>
<td>Ketamine (vs. tramadol)</td>
<td>Launo,80 2004</td>
<td>40/2</td>
<td>†</td>
</tr>
<tr>
<td>Multimodal analgesia</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Opioids, ketorolac, and intraperitoneal/incisional local anesthetics (vs. placebo)</td>
<td>Michaloliakou,42 1996</td>
<td>45/2</td>
<td>†</td>
</tr>
</tbody>
</table>

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.
methodologic quality\textsuperscript{50} 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.\textsuperscript{51}

**Incisional and Intraperitoneal Instillation.** Bisgaard et al.\textsuperscript{19} 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.\textsuperscript{19} No analgesic benefits on visceral pain or shoulder 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.\textsuperscript{19} The findings were later replicated in a similar trial by Lee et al.\textsuperscript{44} In a trial of low methodologic quality,\textsuperscript{52} 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

<table>
<thead>
<tr>
<th>Analgesic Technique</th>
<th>Recommendations</th>
<th>Evidence (Strength)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs/COX-2 inhibitors</td>
<td>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)). 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.</td>
<td>I (A)</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>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.</td>
<td>I (A)</td>
</tr>
<tr>
<td>Opioids</td>
<td>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.</td>
<td>I (B)</td>
</tr>
<tr>
<td>Steroids</td>
<td>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.</td>
<td>I (A)</td>
</tr>
<tr>
<td>Epidural analgesia (and intrathecal LA/morphine)</td>
<td>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)).</td>
<td>I (B)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>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.</td>
<td>I (B)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Current evidence does not support routine use.</td>
<td>IV (D)</td>
</tr>
<tr>
<td>NMDA receptor antagonists</td>
<td>Because of conflicting results from laparoscopic cholecystectomy and other surgical procedures, treatment with NMDA receptor antagonists cannot be recommended.</td>
<td>I (A and B)</td>
</tr>
<tr>
<td>Multimodal analgesic treatment</td>
<td>A combination of intravenous dexamethasone (8 mg) 90 min before operation, perioperative incisional LA, NSAIDs/COX-2 inhibitors, and acetaminophen for 3–4 days may be useful. More data are needed to support this conclusion.</td>
<td>IV (C)</td>
</tr>
</tbody>
</table>

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\textsuperscript{20}: 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 on category IV evidence or extrapolated recommendation from category I, II, or III evidence.

**Table 3. Evidence-based Recommendations for Analgesic Treatment after Laparoscopic Cholecystectomy**
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. 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. In a recent trial of moderate quality, 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.

The valuable analgesic properties of opioids in the treatment of acute, intense postoperative pain after major and minor surgery are well accepted. 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. 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 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 cyclooxygenase and lipoxygenase pathways in the inflammatory response.

A recent review based on available randomized trials (1966 to May 2001) focused on the effects of perioperative single-dose steroid administration. The authors concluded that steroids may have analgesic effects in minor surgical procedures such as hemorrhoidectomy, hallux valgus correction, thyroidectomy, and dental surgery. A recent randomized trial investigated analgesia using a single dose of dexamethasone (8 mg) intravenously given 90 min before laparoscopic cholecystectomy (table 2). 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. However, other studies using a single intravenous dose of 8 mg or 5 mg or a varying dose of dexamethasone in combination with ondansetron 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 and in other surgical procedures 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.

Obviously, concerns about a possible association between steroids and impaired wound healing, postoperative infection, or other complications are important. In a meta-analysis, 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.

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. The efficacy of postoperative epidural analgesia in major surgical procedures is well established. Poor methodologic quality in trials in laparoscopic cholecystectomy have suggested significant analgesic benefits of epidural analgesia and intrathecal morphine/local anesthesia 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.74
In patients undergoing breast surgery,75,76 in patients
undergoing spinal surgery,77 and after abdominal hyster-
ectomy,78 gabapentin (1,200 mg) had clinically important
effects on postoperative pain and morphine con-
sumption. In a recent large-scale, double-blind,
randomized trial of 459 patients undergoing laparo-
scopic cholecystectomy (moderate methodologic qual-
ity; table 2), the analgesic effects of a very low dose of
300 mg oral gabapentin 2 h before operation was com-
pared with 100 mg oral tramadol or placebo.79 Gaba-
pentin 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.79 The effect of timing of administration of
gabapentin has not been studied in laparoscopic chole-
cystectomy.

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

**Clonidine**

Clonidine, an α2 agonist, reduces peripheral sympa-
thetic outflow, inhibits the release of substance P from
the dorsal horn, and suppresses noxious activity at the
spinal cord level.80

Two randomized trials81,82 indicated clinically impor-
tant postoperative analgesic effects using a single 150-μg
or 3-μg/kg dose of clonidine before laparoscopic chole-
cystectomy. 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 lapa-
rosopic cholecystectomy.

In summary, current evidence does not support rou-
tine 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 no-
ciceptive processing and hyperexcitablility.83

It remains unclear whether prophylactic treatment
with NMDA receptor antagonists has a role in the con-
trol of pain after surgery.84,85 In laparoscopic cholecys-
tectomy, the analgesic effects of preemptive NMDA re-
ceptor antagonists have been investigated in five ran-
domized trials of predominantly poor or moderate
methodologic quality (table 2).86–90 In the only trial of
moderate methodologic quality and reporting positive
findings, dextromethorphan (40 mg intramuscular) ad-
ministered 30 min before incision provided significantly
better postoperative pain relief than treatment after sur-
gery and control groups.87–89 In a trial of moderate quality, Mathisen et al.86 found no significant analgesic
effects of a racemic ketamine (1 mg/kg intravenous)
treatment administered 3–10 min before surgical inci-
sion 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,91
major upper gastrointestinal surgery,92,93 cesarian deliv-
ery,94,95 and abdominal hysterectomy96 have suggested
enhanced analgesic efficacy using multimodal analgesic
strategies compared with unimodal analgesic treatment
as assessed by pain, opioid needs, pulmonary dysfunc-
tion, physical activity, mood and sleep disturbances.96

The complexity of pain after laparoscopic cholecystec-
tomy provides rationale for a multimodal analgesic ap-
proach. Michaloliakou et al.42 investigated the effect of a
multimodal analgesic therapy or placebo in a random-
ized trial in 45 patients undergoing laparoscopic chole-
cystectomy (table 2). The treatment group received a
combination of preoperative intramuscular opioid, ke-
torolac, 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. Al-
though not based on randomized comparison, it is note-
worthy that 65–92% of patients receiving a single mode
of analgesic treatment may need supplementary opioids
on the day of laparoscopic cholecystectomy.5,22 Only
20–29% of patients treated with a multimodal analgesic
treatment require supplemental opioids.42,62 However,
in studies by Bisgaard et al.62,97 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.62 The addi-
tion 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 tenoxicam88 or intravenous lidocaine89 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,98,99 metoclopramide [20 mg] vs. ondansetron,100 preoperative carbohydrate beverage vs. placebo,101 and outpatient vs. inpatient laparoscopic cholecystectomy)102 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.103,104 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 intraabdominal pressure allowing adequate exposure is recommended.105 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).97,106

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.7

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 anesthetics107,108 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)9 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 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.

The author thanks Steen Møiniche, M.D. (Department of Anaesthesiology, Glostrup University Hospital, Glostrup, Denmark), for assessing methodologic quality of randomized analgesic trials by Bisgaard et al. cited in the current review.

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