Local Anesthetic Infiltration for Postoperative Pain Relief After Laparoscopy: A Qualitative and Quantitative Systematic Review of Intraperitoneal, Port-Site Infiltration and Mesosalpinx Block

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In a systematic review, we evaluated randomized controlled trials (RCTs) of peripheral local anesthetics (LA) compared with placebo or no treatment in the control of postoperative pain after laparoscopic surgery. A total of 41 trials with data from 2794 patients were considered appropriate for analysis. Of these 41 RCTs, 13 evaluated intraperitoneal LA after cholecystectomy, four RCTs assessed intraperitoneal LA after other procedures, eight RCTs evaluated port-site infiltration after various procedures, 12 RCTs evaluated mesosalpinx or fallopian tube block after sterilization, and four RCTs considered combined LA regimens. Outcome measures were pain scores, analgesic consumption, and time to first analgesic request. Efficacy was estimated by significant difference ($P < 0.05$), as reported in the original reports, and by calculation of the weighted mean difference of visual analog scale pain scores between treatment groups. Improved pain relief was observed in seven of the 13 RCTs of intraperitoneal LA after cholecystectomy and in four RCTs of other procedures. A statistically significant weighted mean difference of −13 mm visual analog scale (95% confidence intervals [CI]: −20 to −6) in favor of the treatment groups was observed after cholecystectomy. Three of eight trials of port-site infiltration showed significant differences but questionable clinical importance and validity in two; weighted mean difference was not statistically significant between treatment groups (95% CI: −9 to 1). All RCTs of mesosalpinx or fallopian tube block after sterilization showed improved pain relief with a statistically significant weighted mean difference of −19 mm (95% CI: −25 to −14) in favor of treatment groups. Data of combined regimens were positive, however, sparse. We conclude that there was evidence for a statistically significant but clinically questionable, important effect of intraperitoneal LA for postoperative pain control. There was evidence for a significant but short-lasting effect of mesosalpinx/fallopian tube block after sterilization, but there was a lack of evidence for any important effect of port-site infiltration. Data from combined regimens were too sparse for conclusions. **Implications:** A systematic review summarizes, through transparent methodology, available information from randomized, controlled trials to produce the best available evidence-based estimate of a "true" clinical effect of an intervention. This systematic review confirms intraperitoneal and mesosalpinx local anesthetic block, not port-site infiltration, to have some impact on postoperative pain after laparoscopy.

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Peripheral use of local anesthetics for postoperative pain relief has become a popular practice in many open surgical procedures. However, the benefit of wound infiltration in open abdominal surgery appears most promising after minor procedures, such as hernia repair; however, it is less beneficial in moderate to major procedures (1,2).

Compared with open procedures, laparoscopic surgery, a minimally invasive technique, is associated with reduced surgical trauma (3,4) and accordingly, is often performed as day-case surgery. Peripheral use of local anesthetics after laparoscopic surgery may therefore, as in the case of minor open procedures, be more likely to provide clinically relevant postoperative pain relief in the early postoperative period. This has been the hypothesis of several trials published in the last decade. However, results from these trials are inconsistent and difficult to overview.

In recent years, several systematic reviews have been published in the field of pain. These reviews

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summarize available information from randomized controlled trials (RCTs) to produce the best available evidence-based estimate of the "true" clinical effect of an intervention.

The purpose of this systematic review is to evaluate the effect of peripherally applied local anesthetics − intraperitoneal instillation, trocar- and port-site wound infiltration, and visceral infiltration/application − on postoperative pain in patients undergoing laparoscopic surgery, by using evidence from all relevant double-blinded, randomized controlled trials.

Methods

We systematically sought reports of RTCs of pain control in laparoscopic surgery with intraperitoneal instillation, trocar- and port-site infiltration, or visceral application of local anesthetics.

Reports were identified by using the Cochrane Library (1999) and the MEDLINE (1966–1999) databases without language restriction. We used different search strategies with free text combinations, including the search terms: "laparoscopy," "laparoscopic," "surgery," "cholecystectomy," "sterilization," "intraperitoneal," "wound infiltration," "incisional," "visceral," "postoperative pain," "local anesthesia," "bupivacaine," "lidocaine," and "ropivacaine." The last search was ultimo May 1999. Additional reports were identified from reference lists of retrieved reports and review articles. No abstracts, correspondences, or unpublished observations were included.

Reports included were double-blinded, randomized comparisons of intraperitoneal instillation, port-site wound infiltration, and visceral infiltration/application of local anesthetics with placebo (saline) and no treatment for postoperative pain treatment after laparoscopic surgery. Only reports considering adult patients (defined as age >15 yr) were included. Studies of open abdominal surgery and direct comparisons of local anesthetic treatment with other treatment modalities as an active control, were not considered.

Each report, meeting the inclusion criteria were read independently by each of the authors and scored by using a three-item, 1–5 quality scale (5). Consensus was subsequently achieved. When the reports were described as randomized, one point was given. An additional point given when the method of randomization was described and adequate (computer generated, table of random numbers, etc.). However, one point was deducted when randomization was inappropriate (alternate randomization, randomization according to weekday, etc.). When studies were described as double-blinded, one point was given, and an additional point given when blinding was described and appropriate (blinded pharmacy manufactured ampules, etc.). However, one point was deducted when blinding was inappropriate. Finally, reports which described the numbers and reasons for withdrawals were given one point. By definition, studies without randomization and blinding were excluded. Thus the minimum score of an included RCT was 2 and the maximum score was 5. Information about type of anesthesia (general, regional), number of patients enrolled, plasma-concentration of local anesthetics, and adverse effects was taken from each report.

The plot of L'Abbé et al. (6) of visual analog scale (VAS) pain scores with local anesthetics compared with a control group was used as a graphic means of exploring the consistency of efficacy and the homogeneity of the data. A scatter of the individual trials lying predominantly to the right of the equality line would suggest efficacy with local anesthetics and relative homogeneity.

Quantitative analysis of combined data was proposed by calculation of the weighted mean difference of VAS early postoperatively between treatment groups, taking into account study size and standard deviations of the VAS scores in the individual trials by using the Review Manager software, version 3.11 (Cochrane Collaboration; The Nordic Cochrane Center, Copenhagen, Denmark). Studies using pain scores other than VAS (e.g., McGill or verbal rating scores) were not included in the quantitative analyses. When data allowed only a qualitative analysis, postoperative effectiveness was evaluated by significant difference ($P < 0.05$ as reported in the original investigation) in pain relief using pain scores (VAS or similar scores), time to first analgesic request, and consumption of supplementary analgesics compared with control. Local anesthetic dosages in positive and negative trials were compared with Mann-Whitney's nonparametric test. Finally, sensitivity of evaluated nonsignificant studies (power of statistical tests) was considered. Any statistical power analysis of individual studies was noted.

We planned to stratify the trials according to the mode of local anesthetic administration (intraperitoneal instillation, trocar- and port-site wound infiltration, visceral application, or combinations), and when possible, to laparoscopic procedure (cholecystectomy, sterilization, etc).

Results

We identified 52 RCTs using local anesthetics (according to inclusion criteria) for postoperative pain treatment in laparoscopic surgery. Of these, we excluded nine studies because of lack of appropriate blinding (7–14) or appropriate randomization (7,9,10,15). Two papers (16,17) were not available through the Danish or other Scandinavian university libraries or through the British Library, leaving 41 reports for analysis.

Appendix 1 gives a full list of studies excluded because of these criteria.

The remaining studies could be divided into 13 trials of intraperitoneal local anesthetics after laparoscopic cholecystectomy, four trials of intraperitoneal local anesthetics after other laparoscopic procedures, eight trials of trocar- and port-site wound infiltration, 12 trials of mesosalpinx/fallopian tube block after laparoscopic sterilization, and four trials with combined local anesthetic regimens in various procedures, all compared with placebo (saline) or no treatment.

We studied 2794 patients, 1510 of whom received four different local anesthetics (bupivacaine, lidocaine, etidocaine, ropivacaine). The range of number of patients included in the studies was 22–300. The median quality score was 3 (range 2–5). Details of included studies are shown in Tables 1- 5. Authors of six papers (18–23) were contacted for provision of dispersion measures needed for the quantitative analyses; however, measures were only obtained in one case (19). Authors contacted regarding their References (24,25) confirmed that patients included in these trials were not identical and that one study (13) was not blinded.

Quantitative, as well as qualitative, analyses were performed on VAS pain scores. For the other outcome measures (supplemental analgesic consumption and time to first analgesic request) only a qualitative analysis was performed because of the variety of analgesics and doses used. Instead, any statistical difference between treatments regarding these outcome measures was extracted from the original reports and documented in table format as done previously for other qualitative systematic reviews (1,26,27).

Intraperitoneal Local Anesthetics for Postoperative Pain Relief After Laparoscopic Cholecystectomy

We identified 13 trials with 18 treatment arms comparing bupivacaine 50–155 mg (in 17 treatment arms) or lidocaine 100 mg (in one treatment arm) with saline (20–22,24,25,28–35) or no treatment (30). In all trials the local anesthetic was administered in the right subdiaphragmatic or gall bladder region in concentrations between 0.1% and 0.5%, 10 and 100 mL at the beginning of the procedure (24,25,28), the end (20–22,25,30–35), or both (24,25,29) (Table 1). Overall, seven of the 13 trials found improved pain relief for at least one of the evaluated pain measures (20,21,24,25,28–30).

In seven trials with 10 treatment arms, overall pain scores, and pain scores for abdominal pain or shoulder-tip pain were significantly reduced compared with the control patients (20,21,24,25,28–30) (Table 1 and Figure 1, top). In most studies, pain scores were only reduced early postoperatively (2–8 h) (20,21,28–30); however, in two trials, reductions lasted up to 24 h (24,25). In the six other trials with eight treatment arms, no effect on pain scores and supplemental analgesic consumption was observed (22,31–35) (Table 1 and Figure 1, top).

Quantitative analysis was performed by using a random effect model, because a test for heterogeneity was significant ($P < 0.001$). The analysis revealed a statistically significant however, clinically small, overall weighted mean difference in VAS scores of −13 mm (95% confidence intervals (CI): −20 to −6 mm) in favor of the treatment groups compared with the control groups (Figure 2, top). However, analysis was only possible with 10 trials (24,25,28–35). In the three other trials (20–22) there were a lack of data (dispersion measures) necessary for calculation of a weighted mean difference. Of these trials, two were positive regarding pain measures (20,21) and one was negative (22), supporting the overall quantitative estimate.

In five studies, supplemental analgesic consumption (most often nonsteroidal antiinflammatory drugs) was significantly reduced to between 60% and 80% during observation periods of 4–24 h (21,24,25,29,30). In the other trials, no effect on supplemental analgesic consumption was observed. No trial evaluated time to first analgesic request.

There was no obvious relationship between achieved pain relief, application site, and dose of local anesthetic. The mean dose of bupivacaine was 112 ± 54 mg (SD) in positive trials and 116 ± 35 mg in negative trials ($P = 0.61$). Pain intensity reports (of importance because it is difficult to detect an improvement in pain if absent or only mild) were not considered to render negative studies insensitive because VAS scores in the control group of most negative studies were >30 mm (22,32,34,35). Appropriate power analysis of the statistical tests was not performed in any of the negative trials.

Intraperitoneal Local Anesthetics for Postoperative Pain Relief After Other Laparoscopic Procedures

Four trials of a variety of procedures (diagnostic and operative gynecological laparoscopy, sterilization, fundoplication, appendectomy, hernia repair, cholecystectomy) evaluated intraperitoneal instillation of bupivacaine 50–100 mg (36–38) or lidocaine 400 mg (36,39) with saline (36–38) or no treatment (39). Table 2 provides more detailed information about the regimens.

All studies showed significantly reduced pain scores with VAS reductions up to 26 mm early, but also up to 24 h postoperatively (36–39). Furthermore, supplemental analgesic consumption was significantly reduced approximately 50% in three (36,38,39)

Table 1. Intraperitoneal Local Anesthetic Instillation in Laparoscopic Cholecystectomy

Study	Quality score	No. of patients treatment/**control**	Bupivacaine mg	Bupivacaine %, volume	Bupivacaine Administered at	Pain scores Overall	Pain scores Abdominal	Pain scores Shoulder	Supplemental analgesic consumption	Comments
Chundrigar et al., 1993 (20)	3	28/**30**	50	0.25%, 20 mL Postop	Region of gall bladder bed	$P<0.05$	$P<0.05$	NS	NS	Significant at 1 and 2 h postop
Pasqualucci et al., 1994 (24)	4	14/14/**14**	100	0.5%, 20 mL Preop	Upper surface of liver, right subdiaphragmatic space, hepatoduodenal ligament, gall bladder	$P<0.05$	–	–	$P<0.05$	Pain scores significant at 4 h in pre-group. and significant at 4, 8, 12, and 24 h in pre- & postgroup
			200	0.5%, 20 + 20 mL Pre- and postop		$P<0.05$	–	–	$P<0.05$	
Pasqualucci et al., 1996 (25)	4	30/30/30/**30**	100	0.5%, 20 mL Preop	Upper surface of liver, right subdiaphragmatic space, hepatoduodenal ligament, gall bladder	$P<0.05$	–	–	$P<0.05$	Significant dose/response relationship: pre + post > pre > post > plac
			100	0.5%, 20 mL Postop		$P<0.05$	–	–	$P<0.05$	
			200	0.5%, 20 + 20 mL Pre- and postop		$P<0.05$	–	–	$P<0.05$	
Szem et al., 1995 (28)	4	26/**29**	100	0.1%, 100 mL Intraop	Right subdiaphragmatic space, subhepatic and gall bladder region	$P<0.05$	–	NS	NS	Significant at 0–6 h
Mraovic et al., 1997 (29)	5	40/**40**	150	0.5%, 15 + 15 mL Pre- and postop	Right subdiaphragmatic space, hepatoduodenal ligament, gall bladder region	$P<0.05$	–	–	$P<0.05$	Significant at ½, 4, and 8 h
Weber et al., 1997 (21)	2	50/**50**	50	0.5%, 10 mL Postop	Subdiaphragmatic space	$P<0.05$	–	–	$P<0.05$	Significant at 2, 6, and 12 h
Tsimoyannis et al., 1998 (30)	3	50/**50**	75	0.25%, 30 mL Postop	Subdiaphragmatic space	–	$P<0.05$	$P < 0.05$	$P<0.05$	Mean pain scores lower up to 12 h
Raetzell et al., 1995 (31)	3	12/**12**	125	0.25%, 50 mL Postop	Subdiaphragmatic, gall bladder bed	NS	–	–	NS	Evaluated at day 0, 1, 2, and 3
Rademaker et al., 1994 (32)	2	15/15/**15**	50	0.25%, 20 mL Postop	Right subdiaphragmatic area	NS	–	–	NS	Evaluated at ½, 1, 2, and 4 h
			100	0.5% (Lidocaine), 20 mL postop		NS	–	–	NS	
Sheinin et al., 1995 (33)	2	20/20/**20**	150	0.15%, 100 mL with adren. postop	Right subdiaphragmatic space	NS	–	NS	NS	Evaluated at day 1–7
			150	0.15%, 100 mL Plain postop		NS	–	NS	NS	
Joris et al., 1995 (34)	2	20/**20**	100	0.125%, 80 mL Postop	Right subdiaphragmatic area	NS	NS	NS	NS	Evaluated at 0, 4, 8, 24, and 48 h
Fornari et al., 1996 (22)	2	50/**50**	100	0.167%, 60 mL Postop	Right subdiaphragmatic space	NS	–	–	NS	Evaluated at 1½, 8, 24, 36, and 48 h
Fuhrer et al., 1996 (35)	4	12/**10**	155	0.375%, 41 mL Postop	Subdiaphragmatic, gall bladder bed	NS	–	–	NS	Evaluated at ½, 1, 2, 3, 6, 12, 24, 36, and 48 h

Intraperitoneal local anesthetic instillation in laparoscopic cholecystectomy. $P < 0.05$ = statistically significant difference between local anesthetic group and control group; NS = no significant difference between local anesthetic group and control group; – = not evaluated. Postop = local anesthetic is administered at the end of the procedure, preop = before the procedure, intraop = during the procedure, plac = placebo, adren = adrenalin.

of the studies. Time to first analgesic request was recorded in only one trial and did not differ between the treatment and control groups (37). Quantitative analysis was omitted because of the different procedures and application sites (subdiaphragmatic or pelvic) investigated.

Table 2. Intraperitoneal Local Anesthetic Instillation in Other Laparoscopic Procedures (Diagnostic Gynecologic, Sterilization, Fundoplicatio, Hernia Repair, Appendicectomy)

Study	Quality score	No. of patients treatment/**control**	Local anesthetic			Pain scores			Supplemental analgesic consumption	Comments
			mg	%, volume	Administered at	Overall	Abdominal	Shoulder		
Narchi et al., 1991 (36)	3	35/**30**	Lido 400 or bupi 100	0.5%, 80 mL 0.125%, 80 mL	Right subdiaphragmatic area preop	–	–	$P<0.05$	$P<0.05$	Pain scores significant at 8, 12, 24, 36, and 48 h
Kelly et al., 1996 (37)	5	27/**30**	Bupi 62.5	0.125%, 50 mL	Pelvic area postop	$P<0.05$	–	–	NS	Pain scores significant at 2 h only. Time to first analgesic request also evaluated NS
Cunniffe et al., 1998 (38)	3	55/**50**	Bupi 50	0.01%, 500 mL	Bilateral subdiaphragmatic postop	–	–	$P<0.05$	$P<0.05$	Pain scores significant at 4 h, 10, and 24 h; Morphine consumption significant over 24 h
Helvacioglu et al., 1992 (39)	3	18/**18**	Lido 100	0.5%, 20 mL	Unspecified intraperitoneally postop	$P<0.05$	–	–	$P<0.05$	Pain scores significant in recovery room only

Intraperitoneal local anesthetic instillation in laparoscopic procedures other than choleystectomy. $P < 0.05$ = statistically significant difference between local anesthetic group and control group; NS = no significant difference between local anesthetic group and control group; – = not evaluated. Postop = local anesthetic is administered at the end of the procedure, preop = before the procedure, Bupi = bupivacaine, Lido = lidocaine.

Trocar and Port-Site Infiltration with Local Anesthetics for Postoperative Pain Relief After Laparoscopic Procedures

We identified eight studies with 11 treatment arms that compared bupivacaine with saline (19,39–44) or no treatment (39,45) (Table 3). Procedures included diagnostic and operative gynecological laparoscopy, cholecystectomy, and hernia repair. The local anesthetic was infiltrated subcutaneously (39,45), subfascially, or preperitoneally (40,41,43), or into all layers of the abdominal wall, including the cutaneous tissues, muscle, and parietal peritoneum (19,42,44). The concentrations used were between 0.125% and 0.5%, in volumes between 5 and 60 mL with a mean dose of 76 ± 48 mg. Infiltration of port sites was performed preoperatively in two (40,42) and postoperatively in nine treatment arms (19,39–41,43–45).

Overall, only three of the eight trials were positive for at least one of the evaluated pain measures (19,40,45). First, improved postoperative pain scores from incisional local anesthetics were observed in only one trial (19) (Figure 1, middle), although Ke et al. (40) and Bilge et al. (45) found a significant difference at the 24 h, not at the one-half, 1, 2, 4, 6, or 12 h assessments (40,45), questioning the validity of these results. Quantitative analysis of five studies using a fixed effect model ($P = 0.3$ in test for heterogeneity) revealed that the weighted mean difference in VAS scores between treatment groups was not significant (−4 mm, 95% CI −9 to 1, Figure 2, middle). Of the three studies not included in the quantitative analysis because of use of McGill pain scores (39,40,43), one study was partly positive (40), and two were negative (39,43). Second, time to first analgesic request was only evaluated in one study with two treatment arms, showing a significant prolongation of between 4 and 6 h compared with saline (40). Third, in one trial, consumption of supplementary analgesics was significantly reduced 24% in the treatment group compared with control (45). In the seven other trials no effect on supplemental analgesic consumption was observed (19,39–44) (Table 3).

No obvious relationship was apparent between application site, dose of the local anesthetic, and degree of obtained pain relief. Mean dose of bupivacaine was 50 ± 0 mg in positive trials and 91 ± 56 mg in negative trials ($P = 0.77$). Low pain scores were not considered to render negative studies insensitive because VAS was >30 mm (or at least moderate according to the McGill scale) in the control groups of most of the negative trials. Power analysis was, however, only performed in two studies (40,42) revealing a 80% power to detect a difference of 15 mm VAS and 1.7 on the McGill scale at the 5% significance level.

Mesosalpinx/fallopian Tube Block with Local Anesthetics for Postoperative Pain Relief After Laparoscopic Sterilization

A total of 12 trials with 14 treatment arms were identified comparing bupivacaine (18,46–50), lidocaine (46,51–54), or etidocaine (23,55) with placebo (18,46,49,50,53–55)

Table 3. Trocar and Port Site Local Anesthetic Infiltration in Various Laparoscopic Procedures

Study	Quality score	No. of patients treatment/**control**	Procedure	Bupivacaine mg	Bupivacaine %, volume	Bupivacaine Administered at	Pain scores	Time to first analgesic request	Supplemental analgesic consumption	Comments
Johnson et al., 1994 (19)	4	40/**40**	Gynecologic	50	0.5%, 10 mL Postop	Parietal peritoneum, preperitoneal, subcutaneously	$P < 0.05$	–	NS	Pain scores significant at 2 h only
Ke et al., 1998 (40)	5	20/19/**18**	Diagnostic gynescologic, sterilization	50	0.5%, 10 mL Preop	Above and below fascia	NS	$P<0.05$	NS	Evaluated at ½, 2, 4 and 24 h ($P < 0.05$ at 24 h for pain scores)
				50	0.5%, 10 mL Postop		NS	$P<0.05$	NS	Supplemental analgesic consumption evaluated over 24 h
Bilge et al., 1997 (45)	2	20/**20**	Laparoscopic cholecystectomy	50	0.5%, 10 mL Postop	Subcutaneously	NS	–	$P < 0.05$	Evaluated at 1, 6, 12, and 24 h ($P < 0.05$ for pain scores at 24 h) Supplemental analgesic consumption evaluated over 24 h
Helvacioglu et al., 1992 (39)	3	18/**18**	Diagnostic gynecologic, sterilazation, other	25	0.5%, 5 mL Postop	Incisional	NS	–	NS	Evaluated in recovery room
Saff et al., 1998 (41)	4	21/**21**	Hernia repair	75	0.125%, 60 mL Post-op	Preperitoneal plane	NS	–	NS	Evaluated at rest and movement at 1, 4, 8, 24, and 72 h
Ure et al., 1993 (42)	2	25/**25**	Laparoscopic cholecystectomy	40	0.5%, 8 mL Preop	All layers of abdominal wall including cutaneous tissue, muscle, parietal peritoneum	NS	–	NS	Evaluated at 5, 24, 30, 48 h and at 2 weeks
Deans et al., 1998 (43)	3	25/25/24/**26**	Hernia repair	100	0.25%, Plain 40 mL	Preperitoneal space	NS	–	NS	Evaluated at 4, 8, 12, and 24 h
				100	0.25%, With adren 40 mL		NS	–	NS	
				200	0.5%, 40 mL Postop		NS	–	NS	
Maier et al., 1994 (44)	2	30/**30**	Gynecologic operative laparoscopy	100	0.5%, 20 mL Postop	Parietal peritoneum abdominal wall, subcutaneously	NS	–	NS	Evaluated after 3, 8, 12, and 24 h

Trocar and port site local anesthetic infiltration in various laparoscopic procedures. $P < 0.05$ = statistically significant difference between local anesthetic group and control group; NS = no significant difference between local anesthetic group and control group; – = not evaluated. Postop = local anesthetic is administered at the end of the procedure, preop = before the procedure.

or no treatment (23,46–48,51,52). The local anesthetic was infiltrated into mesosalpinx (18,46,48,51,54), dripped on the fallopian tubes (23,47,49,50,55), or coated on Filshie clips (52,53). Details about doses (concentration and volumes) can be obtained from Table 4. In all trials, improved postoperative pain relief was obtained in the immediate postoperative period, with significantly reduced pain scores in 13 of 14 treatment arms (Figure 1, bottom) (18,23,46–55), 50% to 70% reduced analgesic consumption in eight of 12 treatment arms evaluating this measure (18,23,46–48,53,54), and prolonged time to first analgesic request in the three studies evaluating this (49,53,54).

Quantitative analysis was only possible with seven of the 12 trials because of the use of McGill or verbal rating pain score (47,50,51), or lack of dispersion measures (18,23). The analysis, performed by using a random effect model ($P < 0.0001$), revealed a significantly reduced weighted mean difference of −19 mm on the VAS scale (CI −25 to −14) in favor of treatment supporting the qualitative estimate (Figure 2, bottom). It should be emphasized, however, that pain relief in general was very short-lived, in most studies lasting for 1–2 h postoperatively.

Regimens with Combined Application Sites of Local Anesthetics for Postoperative Pain Relief After Laparoscopic Procedures

In four trials, various combinations of local anesthetic use was evaluated (Table 5). Cook and Lambert (56)

Table 4. Mesosalpinx/Fallopian Tube Local Anesthetic Infiltration/Application in Laparoscopic Sterilization

Study	Quality score	No. of patients treatment/**control**	Local anesthetic	Administration	Dose	Pain scores	Time to first analgesic request	Supplemental analgesic consumption	Comments
McKenzie et al., 1986 (23)	2	51/**51**	Etido	Dripped on the tubes	0.1% 10 mL	$P<0.05$	–	$P<0.05$	Pain scores significant at 2 h
Alexander et al., 1987 (46)	3	25/25/**25/25**	Lido	Infiltrated in mesosalpinx	1% 5 mL	$P<0.05$	–	$P<0.05$	Pain scores significant immidiatly postop only.
			Bupi		0.5% 5 mL	$P<0.05$	–	$P<0.05$	Comparison with both placebo and no treatment
Kaplan et al., 1990 (47)	3	16/**15**	Bupi	Dripped on the tubes	0.5% 6 mL	$P<0.05$	–	$P<0.05$	Significant in recovery room only
Koetsawang et al., 1984 (51)	3	107/52/**93/48**	Lido	Infiltrated into the tubes	1% 10 mL	$P<0.05$	–	–	Pain scores only significant in 107 patients undergoing open laparoscopy in recovery period, but **not** in 52 patients undergoing standard laparoscopy
			Lido		1% 10 mL	NS	–	–	
Baram et al., 1990 (55)	5	46/**41**	Etido	Dripped on the tubes	1% 10 mL	$P<0.05$	–	NS	Significant at 2 h only
Smith et al., 1991 (48)	3	15/**15**	Bupi	Infiltrated into mesosalpinx	0.5% 6 mL	$P<0.05$	–	$P<0.05$	Pain scores significant at 1 and 4 h, supplemental analgesic consumption significant until 4 h
Barclay et al., 1994 (52)	2	33/**29**	Lido	Coating of Filshie clips	2%	$P<0.05$	–	NS	Significant only at 1 h
Wheatley et al., 1994 (49)	4	30/**30**	Bupi	Dripped on the tubes	0.5% 10 mL	$P<0.05$	$P < 0.05$	NS	Pain scores significant at 1 h only
Ezeh et al., 1995 (53)	5	37/**37**	Lido	Coating of Filshie clips	2% 10 mL gel	$P<0.05$	$P < 0.05$	$P<0.05$	Pain scores significant at 1 h only
Fiddes et al., 1996 (54)	4	29/**30**	Lido	Infiltrated into mesosalpinx	1% 4 mL	$P<0.05$	$P < 0.05$	$P<0.05$	Pain scores significant at 1 and 2 h and 2 h post-discharge
van Ee et al., 1996 (18)	5	20/**17**	Bupi	Infiltrated into mesosalpinx	0.5% 10 mL	$P<0.05$	–	$P<0.05$	Pain scores significant at day 0, 1, and 2. Supplemental analgesic consumption significant until day 1
Tool et al., 1997 (50)	5	27/**32**	Bupi	Dripped on the tubes	0.5% 10 mL	$P<0.05$	–	NS	Pain scores significant at .5 h and discharge

Mesosalpinx or fallopian tube infiltration with local anesthetics in laparoscopic sterilization. $P < 0.05$ = statistically significant difference between local anesthetic group and control group; NS = no significant difference between local anesthetic group and control group; – = not evaluated. Postop = local anesthetic is administered at the end of the procedure, Etido = etidocaine, Bupi = bupivacaine, Lido = lidocaine.

evaluated port-site infiltration plus tubal application of bupivacaine compared with no treatment and found no effect on pain outcome measures (56). On the other hand, three studies comparing port-site infiltration plus intraperitoneal instillation of bupivacaine (57), mesosalpinx infiltration plus intraperitoneal instillation of lidocaine (58), or port-site infiltration plus mesosalpinx infiltration and intraperitoneal instillation of ropivacaine with placebo (59) found significantly reduced pain scores and analgesic consumption

Table 5. Combined Regimens with Local Anesthetic for Postoperative Pain Relief in Laparoscopic Procedures

Study	Quality score	No. of patients treatment/**control**	Procedure	Treatment		Pain score			Supplemental analgesic consumption	Comments
				Administration	Local anesthetic & dose	Overall	Abdominal	Shoulder		
Cook et al., 1986 (56)	3	30/**30**	Laparoscopic sterilization	Trocar and port site infiltration &	Bupi 0.5% 15 mL	NS	–	–	NS	Evaluated at ½, 7 and 17 h
				dripped over the tubes	Bupi 0.5% 10 mL					
Loughney et al., 1994 (57)	4	25/**22**	Diagnostic gynecologic laparoscopy	Intraperitoneal instillation &	Bupi 0.5% 17 mL	–	$P<0.05$	$P<0.05$	$P<0.05$	Evaluated at ½, 1, 2 and 4 h
				Port site infiltration	Bupi 0.5% 3 mL					
Benhamou et al., 1994 (58)	4	25/**25**	Laparoscopic sterilization	Intraperitoneal instillation &	Lido 0.5% 80 mL	–	$P<0.05$	$P<0.05$	$P<0.05$	Pain scores significant at 0, 2, 8, 12, 24 and 36 h
				Infiltrated into each mesosalpinx	Lido 2% 20 mL					
Callesen et al., 1999 (59)	5	39/**41**	Laparoscopic sterilization	Intraperitoneal instillation &	Ropi 0.2% 30 mL	–	$P<0.05$	NS	$P<0.05$	Pain scores significant at 1, 2, 3 and 4 h not later
				Infiltrated into mesosalpinx &	Ropi 0.75% 12 mL					
				Port site infiltration	Ropi 0.75% 18 mL					

Combined local anesthetic use in different laparoscopic procedures. $P < 0.05$ = statistically significant difference between local anesthetic group and control group; NS = no significant difference between local anesthetic group and control group; – = not evaluated. Bupi = bupivacaine, Lido = lidocaine, Ropi = ropivacaine.

up to 4 h postoperatively (57,59) or >24 h after surgery (58). In the study by Callesen et al. (59), extensive use of the rather large doses of ropivacaine (285 mg) virtually abolished postoperative pain, only in the immediate postoperative period and not beyond the expected duration of the local anesthetic. Because of the very different regimens, quantitative analysis was not performed.

Side Effects and Plasma-Concentration of the Local Anesthetic

No side effects or signs of toxicity attributable to the local anesthetic were reported. However, such information was only provided in 12 trials (six trials of intraperitoneal local anesthetic, one of port-site infiltration, three of laparoscopic sterilization and two with combined use of local anesthetics) (25,29–31,33,38,42,46,51,52,58,59). Plasma concentration of local anesthetics was measured in only six studies (31–33,35,39,58). In all cases, plasma concentrations were well below a presumed toxic plasma level of 2–4 μg/mL for bupivacaine and 5 μg/mL for lidocaine (60) except for the study by Fuhrer et al. (35), in which one patient had a maximum plasma bupivacaine concentration of 2.23 μg/mL. Peak plasma concentration was measured between 15 and 30 min after the administration (31–33,35,39) except for one study of combined intraperitoneal and mesosalpinx infiltration in which time to peak plasma concentration was approximately 40 min (58).

Discussion

Although laparoscopic surgery, compared with open procedures, may be associated with diminished surgical trauma response and shortened convalescence (3,61,62), early postoperative pain after laparoscopic procedures is a frequent complaint (63). Peripheral use of local anesthetics for postoperative pain relief is, in this context, an attractive method, which in theory may improve early pain control and minimize the need for opioids. Furthermore, the fact that some laparoscopic procedures are performed on a day-case or a fast-track basis, emphasizes the importance of improving early postoperative pain relief. Accordingly, more than 60 trials of peripheral pain treatment with local anesthetics after laparoscopic procedures have been published. However, despite the substantial amount of published data, results from these trials are difficult to overview because of the variety of clinical settings, drugs, doses, application sites, comparators, and pain outcomes reported.

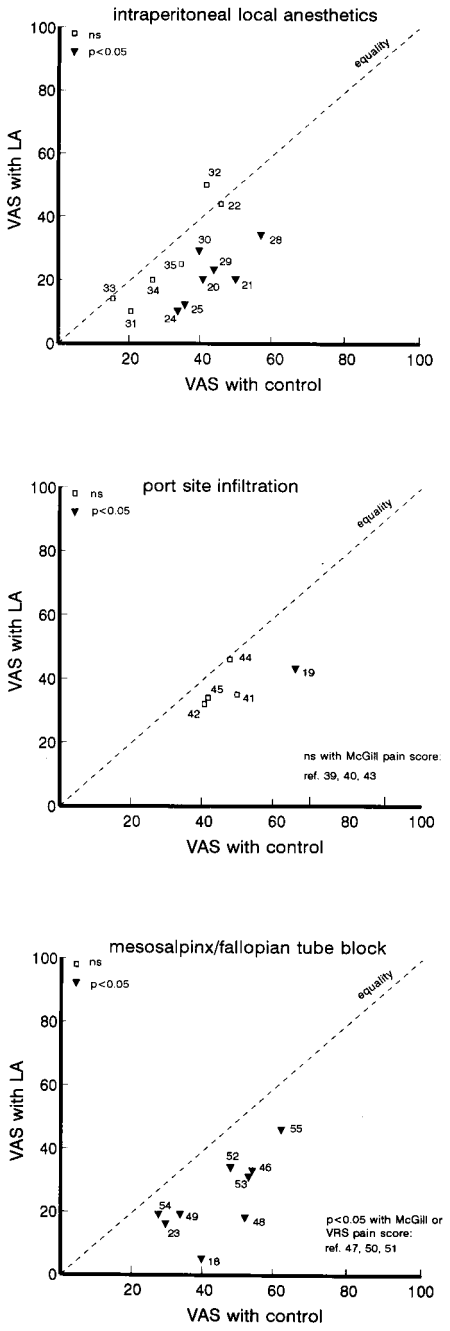

Figure 1. Mean or median visual analog scale (VAS) pain scores early postoperative (1–4 h) for local anesthetic treatment versus control. Each point represents an individual trial (6). Top, Intraperitoneal instillation of local anesthetics (LA) versus control in trials of laparoscopic cholecystectomy. Middle, Port-site infiltration of LA versus control in five studies where VAS scores were available (all except references 39,40,43). Bottom, Mesosalpinx/fallopian tube block with LA versus control in the nine studies where VAS scores were available (all except references 47,50,51). Each square represents an individual study with no significant difference ($P > 0.05$) in pain scores between treatment groups and control groups, and each triangle represents an individual study with significant differences ($P < 0.05$) between groups. Numbers beside the squares and triangles indicate reference number. VRS indicates verbal rating score. Points located to the right of the equality line indicate that visual analog pain scores were higher in the control group when compared with pain scores in the group receiving local anesthetic.

We sought to evaluate the effect of peripheral local anesthetics for postoperative pain relief after laparoscopic surgery compared with placebo or no treatment, given the strict inclusion and exclusion criteria described above. The trials were divided into trials of intraperitoneal instillation, port-site infiltration, mesosalpinx/fallopian tube block, or combined regimens to reduce confounding factors and make comparisons possible.

We chose, in addition to the *qualitative* systematic review, to include a statistical combination of data from the independent results in a *quantitative* analysis. This was done to produce a single estimate of the effect of the intervention, and to help resolve disparities between conflicting studies (64). However, some trials were not included in the quantitative analyses because of lack of data necessary for the calculation, and this may make the results of the quantitative analyses somewhat tenuous. Therefore, the qualitative and quantitative analyses should be viewed together whenever possible, to achieve an overall synthesis of the results from the original trials.

General Comments on Pain

Even within the same type of procedure, pain after laparoscopic surgery may vary in quality and localization and is reported in several trials to be incisional, intraabdominal, or referred (shoulder tip) (65). The etiology is complex, including damage to abdominal wall structures, the induction of visceral trauma and inflammation (34,61,65), and peritoneal irritation because of CO_2 entrapment beneath the hemidiaphragms (66,67). In several trials, attempts have been made to differentiate between the various pain qualities and localizations (21,28,30,31,33,34,36,43); however, the results and conclusions are difficult to interpret, with several authors also expressing difficulties in making this differentiation (43,54). Accordingly, most trials only reported on overall postoperative pain. Furthermore, the literature varies in the reporting of the localization of the most severe pain. Some authors report intraabdominal pain as the most pronounced (20,28,34), although others state incisional (21,42,68) or shoulder-tip pain (36) is the most painful. Ultimately, this may depend on the time course and conditions under which pain is assessed (at rest or during motion). Thus, it was impossible to differentiate regarding pain localization in the quantitative analysis and instead, the reporting of pain in the individual trials was documented in table format.

Intraperitoneal Local Anesthetics

Results from reports of intraperitoneal local anesthetics after laparoscopic surgery revealed weak evidence for an effect on postoperative pain. Especially after laparoscopic cholecystectomy, the evidence was not

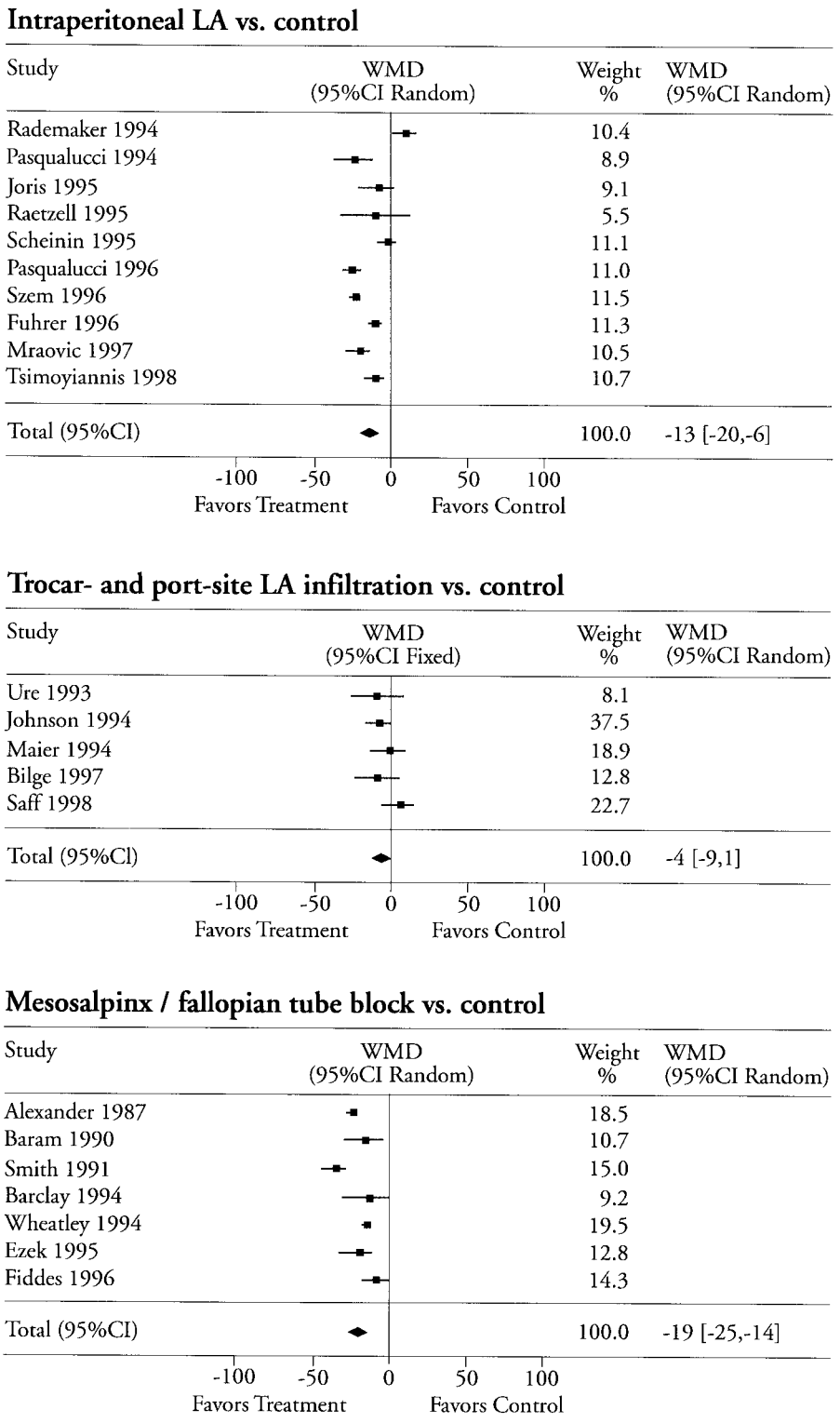

Figure 2. Weighted mean difference (WMD) with 95% confidence intervals (CI) (95% CI, horizontal lines) in visual analog scale (VAS) pain scores early postoperatively (1–4 h) between the local anesthetic groups and control groups in three different regimens. Top, WMD between the intraperitoneal local anesthetic groups and control groups after laparoscopic cholecystectomy. Middle, WMD between the port-site local anesthetic infiltration groups and control groups after different laparoscopic procedures. Bottom, WMD between the mesosalpinx/fallopian tube block groups and control groups after laparoscopic sterilization. Total = results from pooling all trials. Weight = weight of the individual trials in the analysis within each regimen taking into account study size and standard deviations of VAS scores.

compelling, and the clinical significance, at least regarding pain scores, was questionable. The differences between results in the various RCTs are difficult to explain. Although applied doses of local anesthetics did vary, the average dose did not differ between positive and negative trials, and no clear relationship could be extracted regarding effect, dose, and application sites. Pain intensity reports from negative trials were considered adequate and not a cause of possible insensitivity. Furthermore, no major difference was

observed in the quality scores between positive and negative trials of intraperitoneal local anesthetics. The CO_2 insufflation pressure, which may relate to abdominal pain (66,67), did not differ much between trials (ranging 10–15 mm Hg). However, in none of the negative studies was power analysis of the statistical tests performed and small sample sizes in some of these trials (31,32,35) may have rendered these insensitive. One editorial suggested that timing of the local anesthetic administration may be of importance, and that preoperative or pre- *and* postoperative administration should be better than postoperative administration (69). However, although the local anesthetic in all negative trials was administered at the end of the procedure, it was also administered at the end of the procedure in more than one-half of the positive treatment arms, and in only one study was a direct comparison of pre- versus postoperative administration performed (25). Therefore, no firm conclusion regarding timing of the administration can be made. Regarding dosage of the local anesthetic, a significant dose-response relationship was observed in the studies by Pasqualucci et al. (24,25). Therefore, not surprisingly, the amount of local anesthetic used may be of importance.

Port-site Infiltration

Data from the results of incisional local anesthetics did not provide evidence for any important effect of port-site infiltration, either in the qualitative or in the quantitative analysis. Again, no clear differences and relationships were observed in dose and application sites between positive and negative trials. Although there was a general lack of statistical power analysis in negative trials, sample sizes appeared adequate. An obvious explanation would be that intraabdominal pain may blur any possible improvements in incisional pain. However, in a recent trial of a large-dose, somato-visceral, local anesthetic block after laparoscopic cholecystectomy, incisional pain, not intraabdominal or shoulder pain, was reduced, and incisional pain dominated in the control group (68). It may, therefore, be unexpected that no more obvious positive results were obtained. In open abdominal procedures, incisional local anesthetics are most promising after small procedures, such as hernia repair (1), and analogous results might have been expected with the limited somatic trauma associated with laparoscopic surgery. Although not obvious in this review, application site may be of importance, because a previous study showed 20 mL of 0.5% bupivacaine infiltrated subcutaneously and into the parietal peritoneum to be more effective than only subcutaneous infiltration after laparoscopic cholecystectomy (70). In conclusion, there is still no evidence for any major effect of port-site infiltration with local anesthetics.

Mesosalpinx/fallopian Tube Block

From the qualitative and quantitative analyses, evidence was obtained for a mesosalpinx or fallopian tube block to clinically improve pain relief after laparoscopic sterilization in the immediate postoperative period. This has been shown in trials published more than a decade ago and confirmed in trials performed up through the 1990s, although it may be surprising that simply dripping local anesthetics on the fallopian tubes can provide pain alleviation (23,47,49,50,55). The pain relief, although short-lasting, may be of importance, especially because this is often a day-case procedure. On the other hand, the obtainable pain relief also provides dangers and challenges as late postoperative pain may recur after patient discharge, when the possibly ischemia-provoked pain from the fallopian tubes may become aggravated and dominate. Although there is clear evidence for a clinically important effect, the short-duration of this treatment will in most circumstances only postpone, not eliminate, the need for supplemental analgesics, and thus, should only be viewed as a supplement, not a replacement, for other traditional pain treatment.

Combined Application Sites

If only marginal effects are obtainable with intraperitoneal instillation, port-site infiltration, or visceral infiltration *per se*, perhaps combining these techniques would provide clinically relevant pain relief. Three of four trials with different combinations of peripheral local anesthetic use showed improved pain relief early and also up to >24 h after laparoscopy. Only the study by Cook and Lambert (56) showed no effect from port-site and a fallopian-tube block. However, pain was only assessed at one-half, 7, and 17 h postoperatively, and an early effect, within 4–6 h after laparoscopy, may have been overlooked. Most convincing was the study by Callesen et al. (59) in which intraperitoneal instillation, mesosalpinx, and port-site infiltration with a large dose of ropivacaine almost abolished postoperative pain up to 4 h after surgery.

In all of these trials, laparoscopic procedures were gynecological, diagnostic, or sterilization (56–59). Except for one recent paper of a combined somato-visceral local anesthetic block after laparoscopic cholecystectomy (68), in which overall pain and incisional pain was improved up to 4 h postoperatively, there is a lack of data for combined techniques with large-dose local anesthetics in other procedures, and therefore, this is an obvious issue for research.

Side Effects and Plasma Concentration

In less than a third of all reviewed trials, constituting approximately 600 of 2800 patients, information about possible side effects was provided, and in no case

were they attributable to the local anesthetic. However, in no trial were possible side effects a main variable, and this may impair the validity of such information. Even fewer studies provided information about plasma concentrations of local anesthetics, which may, apart from total dosages, depend on site of application (60). However, from reviewed trials, there was only one reported patient achieving a maximum plasma concentration above the presumed toxic plasma concentration of 2–4 μg/mL of bupivacaine after intraperitoneal instillation (60). Therefore, reported doses, ranging up to approximately 150 mg of bupivacaine, may be presumed to be fairly safe. There is, however, a need for more pharmacokinetic data, especially after intraperitoneal use, of large-dose local anesthetics, with and without added epinephrine.

In conclusion there is weak and not compelling evidence for a postoperative analgesic effect of intraperitoneal local anesthetics after laparoscopic cholecystectomy and other laparoscopic procedures. The clinical importance may be questioned. There is a lack of evidence for port-site infiltration with local anesthetics for postoperative pain treatment to have any important pain-reducing effect after laparoscopic surgery. In contrast, there is clear evidence for mesosalpinx block or tubal application with local anesthetics after laparoscopic sterilization to improve postoperative pain immediately after surgery, however, this effect is short-lived. Finally, it appears that combining the various techniques may reduce postoperative pain further; however, data are too sparse for final conclusions. There is also a lack of data for comparing various techniques.

The data presented in this review indicate a need for more large-scale, large-dose pharmacokinetic studies and trials of combined large-dose, somato-visceral local anesthetic block in different laparoscopic procedures to reduce postoperative discomfort. As a part of a multimodal pain treatment it may, together with accelerated convalescence regimens, be possible to gain the full advantage of these minimally invasive techniques.

Appendix 1

Excluded trials, yr (Ref.)	Evaluating	Reason for exclusion	Overall result regarding efficacy
McDonough et al., 1960 (9)	Intraperitoneal local anesthetic	Not randomized and double-blinded	Positive
Berven et al., 1995 (7)	Intraperitoneal local anesthetic	Not randomized	Positive
Kilic et al., 1996 (14)	Intraperitoneal local anesthetic	No information about blinding	Positive
Sarac et al., 1996 (13)	Port site infiltration	Not double-blinded	Positive
Pelland et al., 1977 (10)	Fallopian tube block	Not randomized	Positive
Larsen et al., 1983 (8)	Fallopian tube block	No information about blinding	Negative
Thompson et al., 1987 (15)	Mesosalpinx infiltration	No information about randomization	Positive
Zullo et al., 1998 (11)	Intraperitoneal and port site local anesthetic	No information about blinding	Positive
Pellicano et al., 1998 (12)	Intraperitoneal and port site local anesthetic	No information about blinding	Positive
Hafez et al., 1995 (16)		Not available	
Erenus et al., 1995 (17)		Not available	

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