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REVIEW ARTICLE

Pain after laparoscopy

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Laparoscopy (Greek λαπαρα—flank, or λαπαροσ—soft; σκοπηιν—to look) involves insufflation of the abdomen by gas or other fluid so that the endoscope (usually 6–10 mm in diameter) can view the intra-abdominal contents without being in direct contact with the viscera or tissues. Surgical procedures can be carried out by instruments introduced through one or more additional ports. Laparoscopy therefore defines the surgical approach and is associated with pain which is additional to that caused by intra-abdominal trauma. Nevertheless, pain which occurs after this procedure is significantly less and shorter than that caused by the same surgical procedure made possible by laparotomy.[7 45 50 65 90] The total costs of the procedure are less[32] and the long-term morbidity is less than when performed by laparotomy.[88] The reduction in both pain and loss of function has made possible earlier discharge from hospital,[64] provided that control of residual pain is not by drugs which also prevent discharge because of nausea, ileus or reduction of consciousness and autonomous function.[70 99] Early discharge also reduces the safety of powerful analgesics and makes difficult monitoring and adequate treatment of pain after laparoscopy.

Timing and pattern of pain after laparoscopy

Pain may occur in the upper abdomen, lower abdomen, back or shoulders. It may be transient or persist for at least 3 days.[26 79] Shoulder pain may occur in as many as 63%[78] or as few as 35% of patients.[26] The incidence is not altered if suxamethonium is used to facilitate tracheal intubation.[98] The greatest incidence of pain is in the upper abdomen.[26] Reporting of pain (at any site) is greatest after operation, decreases to a low level within 24 h, but increases to a second or even a third peak later.[2 4 26] Joris and colleagues[46] reported that after laparoscopic cholecystectomy, visceral pain predominates in the first 24 h but subsides from a peak soon after operation, whereas shoulder pain, minor on the first day, increases and becomes significant on the following day.

Mechanism of pain after laparoscopy

This has been reviewed by Schoeffler, Diemunsch and Fourgeaud.[81] Rapid distension of the peritoneum may be associated with tearing of blood vessels, traumatic traction of the nerves and release of inflammatory mediators. The prolonged presence of shoulder tip pain[26 45 78] suggests excitation of the phrenic nerve. This pain is present often after laparotomy[65] and both laparotomy and laparoscopy are associated with persistent pneumoperitoneum, sometimes for 3 days. There is a statistically significant correlation between the width of the gas bubble and pain score,[42] and this pain can be reduced by aspiration of the gas under the diaphragm,[78] by "active aspiration", that is repeated suction and manipulation,[30] by the use of a gas drain[2] or by application of local anaesthesia under the diaphragm under direct vision[71 73] or through a sub-phrenic catheter.[34] Peritoneal inflammation or the presence of gas is probably also the origin of the upper abdominal pain after lower abdominal surgery or after diagnostic laparoscopy. This also can persist for at least 3 days.[26] The use of nitrous oxide instead of carbon dioxide for peritoneal insufflation may not be responsible for the intra-abdominal explosions reported,[41] but it alters insignificantly the incidence and severity of postoperative pain or nausea and vomiting.[43 55] Comyn[18] reported that peritoneal biopsy performed 2–3 days after laparoscopy showed peritoneal inflammation and neuronal rupture, and there was a linear inverse relationship between abdominal compliance at the time of laparoscopy and severity of postoperative pain. Suxamethonium may be used to facilitate intubation and its use can be associated with pain across the shoulders, but its avoidance is not associated with a reduction of pain in the shoulders.[98]

PAIN AFTER LAPAROSCOPIC STERILIZATION

Laparoscopic sterilization is probably the most common operation by laparoscopy in the UK. It is more painful than diagnostic laparoscopy.[29 39] Davis and Millar[23] showed that laparoscopic sterilization pain was worse than that after diagnostic

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Key words

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laparoscopy for the first 4 h after operation but was not significantly greater after hospital discharge on the same day as surgery. Analgesia tends to be given more readily during studies of pain or analgesics than at other times so that the incidence of pain after laparoscopic tubal occlusion is difficult to judge from published studies. In some placebo-controlled studies of postoperative analgesics, some of the patients in the control groups did not receive additional analgesia (see Larsen and Jensen[52]). Nearly all, however, had received some form of intraoperative analgesia.

The three methods of tubal ligation commonly used are diathermy, ring or loop occlusion and clips (e.g. Hulka or Filshie). There is considerable difference in the amount of lower abdominal pain between the methods. Chi and Cole[14] found more pain both during the procedure (under local anaesthesia) and after operation when rings were used than when spring-loaded clips were used. Dobbs and colleagues[26] found that the incidence and severity of lower abdominal pain were significantly higher after ring sterilization than after Hulka clip sterilization and that the pain after clip sterilization did not differ significantly from that after diagnostic laparoscopy. The greatest difference was in lower abdominal pain in the first 6 h after operation. Huang and colleagues[40] found that, under local anaesthesia, tubal diathermy caused more pain than Falope rings but that after 4 h the pain after rings exceeded that of diathermy. Lawson, Cole and Templeton[53] (and Leggat and Barr[54] retrospectively) found that Falope rings were associated with administration of more analgesics than electrocoagulation (diathermy). Comfort and colleagues[17] found that the pain of clips exceeded that after diathermy and others also noted the similarity in character and distribution of colicky pain at and after sterilization with that of dysmenorrhoea.[40]

Pain relief

LOCAL ANAESTHESIA

Pain after diagnostic laparoscopy can be reduced significantly by a bilateral rectus sheath block, performed above the umbilicus with approximately 15 ml of 0.25% bupivacaine on each side.[86]

The pain that follows tubal ligation can be lessened by application of local anaesthetic directly to the fallopian tube or by injection into the mesosalpinx[1 72 85] at operation. This has been shown to have an effect after rings or bands, but also after fulguration or even when applied at the same time, as a gel, as the Filshie clip.[6 48 60 62 75] McKenzie and colleagues[61] reported that 1% etidocaine, when applied to the fallopian tubes from the uterus to the fimbriae, was superior to 0.75% bupivacaine. Its use led to reduced postoperative use of morphine and fewer admissions to hospital overnight.

The total pain of laparoscopy can be reduced by application of local anaesthesia under the diaphragm under direct vision,[73] through an irrigation device[38] or through a sub-phrenic catheter.[34] Shoulder pain after pelvic peritonoscopy can be reduced by either lignocaine or bupivacaine i.p.,[57] and the addition of adrenaline[71] permitted a large volume to be used without approaching systemic toxicity.[87] Conversely, local anaesthetics administered i.p. seem to be ineffective for either visceral or shoulder pain after laparoscopic cholecystectomy[46 77 80] but these studies did not document a head-down tilt to bathe the tissues supplied by the phrenic nerve. However, Schulte-Steinberg and colleagues[82] found that a single injection of interpleural 0.25% bupivacaine 30 ml, but not interpleural morphine 1.5 mg, morphine 1.0 mg i.p. or 0.25% bupivacaine 20 ml i.p., significantly reduced the global pain after laparoscopic cholecystectomy for 6 h in a randomized, double-blind, saline-controlled study of 110 patients. The intraperitoneal drugs were sprayed under pressure over the gallbladder bed and the diaphragmatic surface of the liver. This did not greatly affect the pain perceived in the shoulders. Of patients who received a peritoneal injection, seven of 50 complained of shoulder pain at 6 h, and 24 complained at 24 h. Of those who received interpleural injections, seven of 60 reported shoulder pain at 6 h, and 23 at 24 h. Those reporting shoulder pain were distributed evenly between the treatment and control groups. However, Chundrigar and colleagues,[15] using 20 ml of 0.25% bupivacaine directly onto the gallbladder bed, reported significant pain relief.

Pelvic laparoscopy can be performed under spinal anaesthesia alone, either intrathecally[84] or extradurally,[31] and, in an uncontrolled cohort, caudal extradural anaesthesia provided effective pain relief in children after laparoscopic transperitoneal herniorrhaphy.[91]

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

The amount of pelvic pain after tubal manipulation or tubal ligation may be related to concentrations of prostaglandins. Prostaglandin concentrations are known to increase with dysmenorrhoea. Prostaglandin $PGF_{2\alpha}$ is found in the human oviduct at 10 times the concentration found in plasma. Its localization changes at the time of ovulation. $PGF_{2\alpha}$ is found mainly in the isthmus and correlates with motility of this region, whereas PGE_1 is found in the ampulla.[13 74 94] The human ovarian follicle contains both PGE_2 and $PGF_{2\alpha}$ in critical amounts. Laparoscopic tubal manipulation and ligation release prostaglandins, which may increase the frequency of nociceptive impulses and cause pain. This pain may therefore be amenable to prostaglandin synthase inhibitors. Rarely however, is lower abdominal pain assessed separately from upper abdominal, chest or shoulder pain. Even when it is, pain scores and re-medication may be used for the global pain experience.[2 19 98]

EFFICACY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID)

The prospective, randomized, controlled comparisons of NSAID with placebo which showed that NSAID were superior to placebo in reducing pain or reducing

Table 1 Randomized controlled studies in which NSAID showed more efficacy than placebo after laparoscopy

Reference	NSAID	No. of subjects	Time of dministration	Route	Opioid given to all subjects	Procedure	Pain intensity	Additional analgesic requirements	Time to first pain or analgesic assessment (h)
Davie and colleagues[22]	Fenoprofen 200 mg	45	Postop. prn	Oral	No	Not stated	Reduced	Reduced	
Brodie and Casper[8]	Indomethacin 100 mg	42	Post-induction	Rectal	Yes	Sterilization with rings	Not stated	Reduced	0.5
Huang and colleagues[40]	Paracetamol 1300 mg	50	1 h preop.	Oral	No	Sterilization with diathermy or rings under LA	Reduced	Not stated	1.5
DeLucia and White[24]	Ketorolac 30 mg	50	Preop.	I.m.	Yes	Not stated	Reduced	Reduced	1
DeLucia and White[24]	Ketorolac 60 mg	50	Preop.	I.m.	Yes	Not stated	Reduced	Reduced	1
Comfort and colleagues[17]	Naproxen 550 mg	47	1 h preop.	Oral	Yes	Sterilization with clips or diathermy	Reduced	Reduced	1.5
Gillberg and colleagues[33]	Diclofenac 50 mg	46	1 h preop.	Rectal	Yes	Diagnostic/ sterilization	Reduced	Reduced	0.5
Hovorka and colleagues[39]	Diclofenac 100 mg	99	Post-induction	I.v.	Yes	Diagnostic	Not stated	Reduced	0.5
Liu and colleagues[56]	Ketorolac 60 mg	60	10–20 min preop.	I.v.	Yes	Cholecystectomy	Reduced	Reduced	2
Van Ee and colleagues[93]	Naproxen 500 mg	58	1 h preop.	Rectal	No	Diagnostic	Reduced	Not used	1.5
Green and colleagues[37]	Ketorolac 60 mg	70	30 min pre-recovery	I.v.	Yes	Diagnostic	Reduced	Reduced	0.5
Wilson and colleagues[95]	Diclofenac 75 mg	49	Post-induction	I.m.	Yes	Cholecystectomy	Reduced	No significant difference	
Dunn and colleagues[28]	Naproxen 1000 mg	74	90 min preop.	Oral	Yes	Sterilization with clips	Similar	Reduced	2

Table 2 Randomized controlled studies in which NSAID failed to show more effect than placebo

Reference	NSAID	No. of subjects	Time of administration	Route	Opioid added to both groups	Procedure	Pain intensity of NSAID group	Additional analgesic requirements	Time to pain or analgesic assessment (h)
Mclennan and colleagues[63]	Indomethacin 100 mg	95	1 h preop	Rectal	Yes	Sterilization with clips/rings	Less but $P>0.05$	Similar; $P=0.3$	1.5
Edwards and colleagues[29]	Diclofenac 75 mg	40	Post-induction	I.m.	No	Diagnostic	Less but $P>0.05$	Similar	0.5
Edwards and colleagues[29]	Diclofenac 75 mg	40	Post-induction	I.m.	No	Sterilization with clip	Less but $P>0.05$	Similar	0.5
Crocker and Paech[19]	Indomethacin 100 mg	50	2 h preop.	Rectal	Yes	Sterilization with clips	Less but $P=0.07$	Less but $P=0.07$	2.5
Hovorka and colleagues[39]	Diclofenac 100 mg	70	Post-induction	I.v.	Yes	Sterilization	Not stated	Similar	0.5
Shapiro and Duffy[83]	Ketorolac 30 mg	40	Post-induction	I.m.	Yes	Sterilization with clips	Less but $P>0.05$	Less but $P>0.05$	0.5
Windsor and colleagues[96]	Tenoxicam 20 mg	67	At induction	I.v.	Yes	Diagnostic	Less but $P>0.05$	Less but $P>0.05$	0.5

the requirement for additional analgesic after laparoscopy are shown in table 1. Those which showed no significant benefit of NSAID compared with placebo are shown in table 2.

COMPARISON OF NSAID WITH OTHER ANALGESICS FOR THE PAIN AFTER PELVIC LAPAROSCOPY

Randomized, controlled comparisons of NSAID with other analgesics are shown in table 3. NSAID have been compared with paracetamol, codeine, oxycodone, fentanyl, morphine, pethidine, dexmedetomidine and dezocine.

Comparison with paracetamol[40] showed that meclofenamate was more effective in reducing the pain of tubal ligation during and after local anaesthesia, although both drugs were insufficient in most cases. However, both drugs were given 1 h before operation and peak concentrations of oral paracetamol were achieved at approximately 1 h in plasma and at 4 h in CSF,[5] so that maximal analgesia would not have been achieved at the time of surgery.

Dexmedetomidine was effective in reducing the need for other analgesia but was distinguished by increased somnolence and bradycardia, such that 33% of such subjects required atropine.[3] Dezocine was associated with a higher incidence of nausea or vomiting (60%) than either ketorolac or fentanyl, and most of the dezocine subjects required antiemetic therapy.[25] In a comparison of zomepirac 100 mg with codeine 60 mg[27] for the pain of sterilization with diathermy or rings, there was little difference in pain intensity or additional opioid requirements. Zomepirac has since been withdrawn because of the incidence of NSAID-related side effects. Ketorolac 30 mg i.m. has been compared with pethidine 100 mg i.m. after induction of anaesthesia.[11] Duration of operation was not stated, but at 30 min after operation those who had received pethidine had only marginally less pain, at 1 h there was no difference, and at 4 h after operation the

Table 3 Randomised controlled comparisons of effects of NSAID and other analgesics on pain after laparoscopy

Reference	NSAID	No. of subjects	Time of administration	Route	Opioid given to all subjects	Procedure	Comparator	Pain intensity	Additional opioid equirements
Davie and colleagues[22]	Fenoprofen 200 mg	43	Postop. when required	Oral	No	Not stated	Morphine 8 mg i.m.	Increased	Similar
Dunn and colleagues[27]	Zomepirac 100 mg	48	30 min preop.	Oral	No	Sterilization with diathermy/rings	Codeine 60 mg orally	Similar	Similar
Huang and colleagues[40]	Meclofenamate 100 mg	50	1 h preop.	Oral	No	Sterilization with diathermy/rings	Paracetamol 1300 mg orally	Reduced	Not stated
Huang and colleagues[40]	Meclofenamate 200 mg	50	1 h preop.	Oral	No	Sterilization with diathermy/rings	Meclofenamate 100 mg	Similar	Not stated
Rosenblum and colleagues[79]	Ibuprofen 800 mg	30	1 h preop.	Oral	No	Diagnostic laparoscopy	Fentanyl 75 μg	Similar	Similar
Aho and colleagues[3]	Diclofenac 250 μg kg^{-1}	48	Postop. when required	I.v.	No	Sterilization with clips	Oxycodone 60 μg kg^{-1} i.v.	Increased	Increased
Aho and colleagues[3]	Diclofenac 250 μg kg^{-1}	48	Postop. when required	I.v.	No	Sterilization with clips	Dexmedetomidine 0.4 μg kg^{-1}	Increased	Increased
Grace and colleagues[35]	Diclofenac 75 mg	80	Pre-induction	I.m.	No	Sterilization with rings	Fentanyl 100 μg	Increased/ decreased	See text
Ding and White[25]	Ketorolac 60 mg	88	Pre-induction	I.v.	Yes	Not stated	Fentanyl 100 μg	Reduced	Reduced
Ding and White[25]	Ketorolac 60 mg	92	Pre-induction	I.v.	Yes	Not stated	Dezocine 6 mg	Similar	Similar
Cade and Kakulas[11]	Ketorolac 30 mg	60	Post-induction	I.m.	Yes	Sterilization	Pethidine 100 mg	Reduced	Reduced
Lysak and colleagues[58]	Ketorolac 60 mg	56	30 min	I.m.	Yes	Not stated	Fentanyl 100 μg	Reduced	Similar
Lysak and colleagues[58]	Piroxicam 40 mg	55	90 min preop.	Oral	Yes	Not stated	Fentanyl 100 μg	Reduced	Similar

ketorolac group had significantly less pain than the pethidine group.

Both of these groups were given fentanyl during operation and this technique was used in a large minority of the comparisons.[11 25 35 58] When fentanyl was given during operation, either as a single bolus or as cardiovascular changes indicated, and sufficient time elapsed before assessment of analgesia, ketorolac[25 58] reduced postoperative pain more than fentanyl alone. When NSAID were the sole analgesics for sterilization, they were less effective than morphine[22] or oxycodone.[3] For diagnostic laparoscopy without sterilization, ibuprofen and fentanyl were equally effective.[79] In a double-blind, double-dummy study of 80 patients undergoing sterilization with Falope rings, diclofenac i.m. was compared with fentanyl i.v.[35] At approximately 40 min after administration of diclofenac and 30 min after fentanyl, less pain was associated with fentanyl. However, 30 min later, in those requesting additional analgesia, the fentanyl group reported more pain. Perhaps more significantly, most pain scores in the first 2 h after operation were unsatisfactorily high (authors' own comment) and the scores of those who requested additional analgesia were not always higher than those who did not. The time to the first analgesic, when given, was also similar in both groups.

These results suggest that NSAID in usual therapeutic doses are more effective than paracetamol. They also suggest that analgesia associated with NSAID was broadly similar to that of short-acting opioids such as pethidine or fentanyl provided that the assessment is made around the peak action of the NSAID or at the end of the duration of action of the opioid. The combination of an NSAID and a short-acting opioid is more effective in intensity and duration than the short-acting opioid alone. However, comparisons of diclofenac with oxycodone and fenoprofen with morphine showed that the longer-acting opioid was clinically significantly more effective.

NSAID AND POST-LAPAROSCOPIC CHOLECYSTECTOMY PAIN

Wilson and colleagues[95] investigated diclofenac 75 mg i.m. at induction of anaesthesia compared with placebo. Intraoperative fentanyl 3 μg kg^{-1}, with supplements as required, was used in all patients. A second dose of the drug was given after 12 h and morphine was given as required. Pain was scored on a visual analogue scale at 4, 24 and 48 h after operation. In the diclofenac group, pain was significantly less at 4 h and there was a lower consumption of morphine (ns).

Liu and colleagues[56] gave ketorolac 30 mg, 15 min before induction, another 30 mg after intubation and 60 mg 4 h after operation, and compared ventilatory, recovery and analgesic effects with saline. Duration of anaesthesia was approximately 2 h. Significantly lower pain scores were recorded in the ketorolac group. One-third of the ketorolac group and two-thirds of the saline group required additional postoperative analgesia. There was no significant difference in anxiety, sedation or nausea between the two groups. There was also no difference in the severity of ventilatory dysfunction.

The undisputed success of NSAID in this operation relative to pelvic laparoscopy may be because the pain was relatively more dependent on inflammatory mediators, because the operation was longer and more intraoperative analgesics were given, or because there was a longer time from administration to assessment of the NSAID.

FAILURE OF NSAID TO PROVIDE MORE PAIN RELIEF THAN PLACEBO

There appears to be wide variation in efficacy of NSAID on pain after laparoscopy. Some randomized, double-blind, controlled studies showed insignificant effects, although none suggested that NSAID were less effective than placebo. This lack of efficacy is contrary to the numerous studies which demonstrate a convincing analgesic effect or opioid-sparing effect of NSAID for the pain of more invasive surgery[12 20 69 92] in which pain scores were used and opioid use was measured by patient-controlled analgesic administration.

MacLennan and colleagues[63] showed that there is an insignificant reduction in the numbers of patients requiring pethidine, and in the amount of pethidine given, in those who received an indomethacin suppository 1 h before operation compared with those who had a dummy suppository. Almost 100 patients took part, but the method of determining the analgesic efficacy may not have been sensitive enough. The recovery room nurses, who were unaware of the preoperative medication, gave either pethidine or a combination of paracetamol and codeine for postoperative pain at their discretion and at apparently different doses. Only pethidine consumption was recorded and pain was not scored. The method was unable to detect a difference in pain levels caused by clip or ring sterilization.

Edwards and colleagues[29] also demonstrated a lower pain score after laparoscopic sterilization at 20 min and 1 h and 20 min after diclofenac i.m. (compared with no injection) and, although the median of one pain score was more than 3 SEM less than the other, the difference between the two groups of 20 patients was not significant.

Significantly reduced opioid requirements after diclofenac 75 mg for diagnostic laparoscopy but not for laparoscopic sterilization have been reported,[39] although even in the latter procedure, the diclofenac group required slightly less fentanyl and paracetamol after operation. Perhaps a lack of difference or lack of sensitivity can be found in the method of pain titration and in the timing of assessment. Pain was not scored. Analgesics in large aliquots (fentanyl 50 μg i.v. or paracetamol 0.5 g rectally) were given "according to clinical judgement". Observer scores of pain were usually less than those of the patient and there would be reluctance to use additional large doses for small increases in pain. Diclofenac was given after induction of anaesthesia and approximately 27 min before the end of anaesthesia, possibly 30 min before the first assessment of pain and analgesic requirements. However, Green and colleagues were also able to detect a differential benefit for NSAID after diagnostic laparoscopy[37] but not after laparoscopic sterilization.[36]

Prados and Blaylock[76] found no benefit of ketorolac 30 or 60 mg given 15–20 min before the end of surgery, as tested by the use of patient administered and controlled fentanyl. Ketorolac was given i.m. and titration of analgesic to pain in the recovery room might be expected to be achieved without the influence of ketorolac but the amount of analgesic self-administered during admission was only marginally reduced in the ketorolac 60 mg group and not in the ketorolac 30 mg group.

Windsor and co-workers[96] found a non-significant improvement in pain score and a reduction in the number of rescue doses of fentanyl after tenoxicam i.v. at induction of anaesthesia. Pain and pain rescue were measured over 24 h. Tenoxicam is slow in analgesic onset and the peak action may be too late to treat pain susceptible to NSAID.

Although the provision of pain relief in the recovery period is variable and the efficacy of analgesics is dependent on patient expression of

Table 4 Assessment of pain and analgesic requirement in randomized controlled comparisons of NSAID and placebo

Reference	Significant effect of NSAID found	Assessment of pain	Assessment of additional analgesic requirement
Mclennan and colleagues[63]	No	Not stated	Amount and type given on discretion of staff
Edwards and colleagues[29]	No	Visual analogue scale (VAS)	Paracetamol, co-proxamol or pethidine given by nurse on request by patient
Edwards and colleagues[29]	No	Visual analogue scale (VAS)	Paracetamol, co-proxamol or pethidine given by nurse on request by patient
Crocker and Paech[19]	No	VASat 0.5, 1 and 3 h	Pethidine 25 mg doses i.v. titrated to patient comfort
Hovorka and colleagues[39]	No	Three-point rating scale assessment by observer	Paracetamol or fentanyl given on observer's judgement of pain
Shapiro and Duffy[83]	No	VAS at 1 and 5 h, peak VAS	Standard protocol: amount recorded
Windsor and colleagues[96]	No	Linear analogue scale and verbal rating scale	Patient request to nurses and pain diary
Davie and colleagues[22]	Yes	Linear analogue scale (LAS) + interview	Patient demand when tolerance exceeded
Brodie and Casper[8]	Yes	Nurse's judgement of analgesic need	Standard protocol of variable analgesia (not double-blind)
Huang and colleagues[40]	Yes	1–5 verbal rating scale	Morphine, meclofenate or paracetamol
Delucia and White[24]	Yes	0–100 las (averaged)	Fentanyl or ketorolac used as rescue analgesia
Delucia and White[24]	Yes	0–100 las (averaged)	Fentanyl or ketorolac used as rescue analgesia
Comfort and colleagues[17]	Yes	VAS at 1 and 2 h	Amount of paracetamol, codeine, pethidine or morphine determined by nurse
Gillberg and colleagues[33]	Yes	10 cm visual analogue scale (VAS)	Pethidine or paracetamol given by nurse
Hovorka and colleagues[39]	Yes	Three-point rating scale assessment by observer	Paracetamol or fentanyl given on observer's judgement of pain
Liu and colleagues[56]	Yes	VAS at 30, 60 90 min postop.	Standard protocol of different analgesics
Van Ee and colleagues[93]	Yes	0–10 numerical rating scale	Paracetamol/naproxen provided on patient request
Green and colleagues[37]	Yes	10 cm visual analogue scale (VAS)	Incremental i.v. doses of fentanyl 25 μg
Wilson and colleagues[95]	Yes	10 cm visual analogue scale (VAS)	Morphine 10–15 mg prn
Dunn and colleagues[28]	Yes	Five-point verbal rating scale in recovery and at 2 and 4 h	Mefenamic acid and/or diamorphine on nurse's judgement

demand or nurses' perceptions of pain, even before pain severity is scored, the same objections apply also to those studies in which a significant analgesic effect for NSAID was found (table 4).

NSAID AND SHOULDER PAIN

If the pain perceived in the tips of the shoulders is related to inflammation of the peritoneal reflections supplied by the phrenic nerve, this may also be reduced by anti-inflammatory analgesics.

Although Crocker and Paech[19] found that global pain after laparoscopy and mean requirements for pethidine were less after indomethacin than after placebo ($P=0.09$ or 0.07), shoulder and chest pain was higher in the indomethacin group. Van Ee, Memrika and Van der Linden[93] gave naproxen 500 mg or dummy suppository 1 h before laparoscopy. The control group required more additional analgesics and had higher pain scores than the naproxen group, but the incidence of shoulder tip pain was not different in the two groups. Edwards and colleagues[29] studied women who had undergone either diagnostic laparoscopy or laparoscopic tubal ligation. In each group, patients were given diclofenac 75 mg after induction or no injection. Shoulder pain was noted separately but analgesia was given for total pain. The laparoscopic sterilization group had, on average, significantly more pain than the diagnostic laparoscopy group. Pain scores were lower in the diclofenac group on each assessment but the differences were not significant.

TIMING

The timing of NSAID administration and onset has been reviewed by Moote.[69] There is clearly a latency in onset of analgesic action and a longer delay before peak action. Rosenblum and co-workers[79] showed that the analgesic effect of ibuprofen was apparent only after the patient had left the recovery room. Davie, Slawson and Burt[22] gave oral fenoprofen 200 mg and saline injection when patients complained of pain in a double-blind, double dummy, placebo-controlled study. The assessment was an interview and a 10-cm linear analogue scale. Although those who received fenoprofen had less pain than those who received placebo after 1 h, the difference was not significant until 2 h. Van Ee, Memrika and Van der Linden[93] found naproxen to be more effective than placebo only 30 min after operation, or approximately 2 h after administration of the naproxen suppository.

In the studies which failed to demonstrate a significant analgesic effect of NSAID, the drug was usually given at or after induction of anaesthesia, that is approximately 30 min before rescue analgesia was available for pain in the recovery room, except where indomethacin was administered rectally 1 or 2 h before operation.[19,63] In those in which more than one assessment of pain or analgesic consumption was made, the greatest difference between NSAID and placebo effect was found at 2.5, 4 or 5 h after i.v. or i.m. administration. Similarly, in those studies in which NSAID demonstrated a significant analgesic effect, the greatest effect was found between 2 and 24 h after administration. Dunn, Clark and Jones,[28] using a relatively large dose of the long-acting agent naproxen did not find variation in analgesia with time over the first 24 h.

After oral obsorption, there is a delay to peak plasma concentrations of most NSAID of approximately 1–2 h.[89] There may be further delay before peak concentrations at the site of action are reached. For example, regional concentrations of prostanoids within the fallopian tube suggest that surface generation may be less than in the lamina propria, for example. The data sheet for ketorolac (1996–1997) states that "the time to onset of analgesia effect after both intravenous and intramuscular administration is similar and is approximately 30 minutes with maximum analgesia occurring within one to two hours". (The evidence for this statement is difficult to trace in any single study, either by literature search or by direct enquiry to the information service at Syntex (Roche).) Similar data for the peak analgesic effect of i.v. diclofenac are not readily available but the same delay would be expected.[44] Pain assessment and analgesic administration may be occurring before NSAID become effective. It might be argued that NSAID were delayed in onset because they had no effect against prostanoids already synthesized.[69]

Another mechanism may be operative. It is possible that accumulation of the "right-handed" stereoisomer (R enantiomer) may be responsible for the build-up of analgesic effect. The S enantiomer of most (if not all) NSAID shows more anti-inflammatory activity than the R enantiomer, yet the analgesic activity of flurbiprofen for example, is related to both the R and S enantiomers, and prostaglandin inhibition within the brain is significantly inhibited by the pure R enantiomer.[9] Although many NSAID show one-way conversion of R to S enantiomer, via acetyl co-enzyme A for example, this is not universal or (with the exception of ibuprofen) extensive. One-way conversion does not occur with ketorolac in humans[67] but the R form has a half-life approximately twice that of the S form and would accumulate with repeated doses and dominate with time.

NSAID might provide pre-emptive analgesia. A noxious stimulus causes spinal and supraspinal processing, such as "wind-up" at the NMDA channel in the spinal dorsal horn, thereby increasing the throughput of the second-order spinal pain transmission neurones from a given input from the nociceptor through the first-order C fibre nociceptive afferent. If effective analgesia is present before the nocigenic stimulus, there is less wind-up and the total pain experience and total amount of analgesia required is less.[97] However, the pain of the early postoperative period, either by moderate or strong nocigenic stimuli or by mechanical, thermal or noxious stimuli in the presence of inflammation and hyperalgesia, can also cause wind-up.[49] Comparison of the effect of diclofenac given before laparoscopy with that diclofenac given after did not show any difference in pain or analgesic requirements in the postoperative period.[10] Although allowance was

made for the time required for diclofenac to exert its analgesic effect, it did not take into account the nocigenic stimuli in the early postoperative period.

ELIMINATION OF BIAS

In 1983, Dunn and colleagues[27] compared premedication with zomepirac 100 mg, an obsolete NSAID, with codeine 8 mg for prevention of pain after dental extraction and laparoscopy. The assessments of the procedures were considered separately. The study was prospective, randomized, double-blind and double-dummy, and assessments were a 10-cm vertical linear analogue scale and a five-point verbal rating scale. Systemic and local analgesics, with the exception of nitrous oxide, were not used in the general anaesthetic technique. Rescue analgesia was available. Analysis of those who required rescue medication was separated from those who did not. At 5 h after operation, all but one patient in the codeine group had received additional analgesia. Pain scores and rates of re-medication in each group were similar and only by 4 h was there a moderate, but not significant, difference in favour of zomepirac. (Pain scores and rates of re-medication in dental patients suggested that zomepirac was significantly more effective.) The study was not subjected to analysis to estimate the likelihood of demonstrating a difference between the two treatment groups but, in other respects, it achieved a higher standard of objectivity than most that followed. The subsequent study of Brodie and Casper,[8] which has been cited and discussed by almost half of the reports of the randomized studies that followed, was not double-blind (the treatment being dependent on the last digit of the hospital number), nor was pain assessment objective.

Only before the studies of Dunn, Clark and Jones[28] and MacLennan and co-workers[63] was the sample size calculated to achieve an 80% probability of detecting a material difference between the two groups of pain scores or between the numbers requiring analgesia. However, the numbers of patients in the studies which showed NSAID to be superior to placebo were not materially greater than those in studies which failed to show a significant effect.

There are many other studies and reviews or audits of the efficacy of analgesics for pain after laparoscopy, but only randomized controlled studies are included here.

ASSESSMENT OF OUTCOMES (SEE ALSO TABLE 4)

Almost all studies described have used patients' assessments of pain, either with a linear analogue scale, some other form of visual analogue scale, numerical rating scale or with a verbal rating scale. Verbal rating scales show a high level of correlation with linear analogue scores.[51] Occasionally, pain scores were treated not as ordinal data but subjected to parametric analysis and averages compared.[24] This may be defensible.[51] Prados and Blaylock[76] used fentanyl by patient-controlled administration to determine analgesic requirements after outpatient gynaecological surgery which required intubation and ventilation. Unfortunately, the report does not state that all were laparoscopies. However, in one study[8] the method of pain scoring was left to a nurse in recovery and the investigators were not blinded. In another,[63] a large, randomized, double-blind, double-dummy study, with pre-study power analysis, no assessment of pain was made by the patient and two types of rescue analgesia were administered according to patient demand and staff discretion. The study was unable to show any differences between the pain of tubal occlusion by clips and that with rings, as demonstrated by others[14 26]

REVIEW OF REVIEWS

There have been many reviews of NSAID in general, and individually, with regard to their pharmacology, uses and efficacy; few have considered their place in postoperative pain after laparoscopy[16 47 69] and even fewer have adequately considered analgesic requirements in reviews of laparoscopy.[81] The former have described the divergence of opinion of efficacy in comparison with either placebo or with other analgesics. They have commended for consideration the concept of balanced analgesia although there is little evidence for potentiation of quantity or quality of analgesia after laparoscopy and there is evidence of the disadvantage of a greater range of unwanted side effects. Only Schoeffler, Diemunsch and Fourgeaud[81] considered the different types of pain, different mechanisms and some of the various strategems for overcoming them.

THE PLACE OF NSAID FOR POST-LAPAROSCOPY PAIN

That NSAID are most appropriate for pain after laparoscopy has not been proved. Even the additional pain caused by tubal ligation, possibly mediated by prostaglandins, does not appear to be ideally treated by prostaglandin synthase inhibitors. In one study, pain was relieved better after diagnostic laparoscopy and in another after tubal ligation. Does reduction in opioid use have a clinical advantage? Except in rare cases the need for opioids, especially when given judiciously and frequently, is unlikely to compromise ventilation. The reduced need for opioids is often postulated to reduce nausea and vomiting, ileus and time to readiness for discharge. Yet, usually no difference is found in the times of recovery to the various stages of autonomous function. Nausea and vomiting accompany the pain of both tubal occlusion and dysmenorrhoea[40] and may be unrelated to the use of opioids. Conversely, the antiemetic advantage of propofol for day-case anaesthesia is reduced or lost when papaveretum or morphine is used.[59 66 68] It would seem necessary to administer NSAID 1 h or more before laparoscopy to gain the maximum benefit after operation. At this stage, the accentuated risks of refractory bleeding, hypovolaemia or renal failure are not yet apparent. Bleeding is more difficult to detect and control during laparoscopy than laparotomy. Some studies and other reviews[16] have suggested that the quality of analgesia and patient

satisfaction is improved if both NSAID and opioids are used. However, Davie and Gordon[21] have shown that fenoprofen and paracetamol used alone in modest doses were not significantly more effective than placebo, but in combination were significantly superior. This combination would appear to be more suitable for day surgery than the addition of opioids. Despite all the above, it is possible that the measures of pain, usually at rest rather than on movement, and well-being, are too insensitive and that the clinical impression of the nursing staff, based on the summation of many visual and verbal stimuli, should be quantified and tested. It is equally possible that the perception of pain relief by NSAID is an extrapolation from operative models in which NSAID have a more noticeable effect.

Conclusion

Pain which is caused by laparoscopy and laparoscopic surgery is variable in duration, severity and character. The tendency towards reduced hospital stay for laparoscopic procedures leads to failure of recognition and treatment of pain which arises or increases after the first few postoperative hours. Pain which is severe after hospital discharge makes necessary high-cost domiciliary visits and possibly inadequate treatment because of the constraints of the lack of monitoring.

Local anaesthetic techniques, regional or focal, appear more successful for pelvic laparoscopy than for laparoscopic cholecystectomy for example, although interpleural anaesthesia may be effective and safe for unilateral pain. Pain related to stimulation of the phrenic nerve is not easily resolved by extradural anaesthesia without considerable risk or life support.

Non-steroidal anti-inflammatory drugs and paracetamol are not as effective for immediate postoperative pain as are opioids and appear to be ineffective for pain in the shoulders. Their effect in the majority of patients is to reduce the severity of pain or to reduce the need for opioid analgesia. As a sole analgesic, they appear inadequate in most patients. The evidence that the use of NSAID increases recovery or hospital discharge is not consistent. Single intraoperative doses of short-acting opioids such as fentanyl are also inadequate for pain in most cases. However, in many patients, NSAID, given sufficiently early to be effective by the time of waning of the effect of the peroperative opioid, are sufficient to render discomfort tolerable.

Until the various pains are assessed separately and analgesic stratagems are assessed for the different components of the pain experienced, most of these pain-relieving methods will be ineffective because the remaining pain is a sufficient cause of dissatisfaction to maintain demands for rescue analgesia and to increase pain scores. A combination of simple measures, such as evacuating the insufflated gas, application of local anaesthetic gel to the fallopian tubes at the time of clipping, use of a rectus sheath block or local anaesthetic applied to skin and muscle wounds, preoperative use of paracetamol and use of a moderately short-acting intraoperative opioid may reduce the immediate and referred pain effectively and safely. The later inflammatory pain can then be modified with non-opioid drugs such as the anti-inflammatory agents.

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