Analgesia following appendicectomy - the value of peritoneal bupivacaine

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Purpose: Peritoneal inflammation is an important feature in many patients presenting with appendicitis. The contribution of peritoneal nerve fibres to pain experienced after appendicectomy has received little attention.

Method: In this prospective double blind randomized study a consecutive series of 60 patients undergoing appendicectomy for suspected appendicitis were enrolled. A dose of 1.5 $mg \cdot kg^{-1}$ bupivacaine 0.5 % was used. Group one patients received the entire dose of bupivacaine subcutaneously. Group two patients received half the dose subcutaneously (sc) and half the dose to the peritoneum. Pain scores were assessed pre-operatively and at 30 min, 12 and 24 hr post-operatively using a visual analogue scale. Time to first analgesia and total analgesia requirements in the first 24 hr were recorded.

Results: The patients receiving the sc combined with peritoneal bupivacaine had a lower pain score 30 min post-operatively (32 ± 2 *vs* 54 ± 4; $P < 0.0001$), a longer time to first analgesia (248 ± 20 *vs* 164 ± 17 min; $P = 0.002$)as well as lower opioid (68 ± 5 *vs* 100 ± 7 mg; $P = 0.0002$) and non steroidal analgesic requirements (65 ± 6 *vs* 96 ± 6 mg; $P = 0.007$) in the first 24 hr post-operatively.

Conclusion: A combination of sc and peritoneal infiltration with bupivacaine is superior to skin infiltration alone in the relief of pain post appendicectomy.

Objectif : L'inflammation péritonéale est un signe important chez de nombreux patients souffrant d'une appendicite. La participation des fibres nerveuses du péritoine à la douleur éprouvée après l'appendicectomie n'a jamais vraiment retenu l'attention.

Méthode : Une série de 60 patients consécutifs suspects d'appendicite et devant subir une appendicectomie ont été inclus dans une étude prospective, en double insu et randomisée. Une dose de 1,5 $mg \cdot kg^{-1}$ de bupivacaïne 0,5 % a été utilisée. Les patients du premier groupe ont reçu la dose complète en infiltration sous-cutanée. Ceux du deuxième groupe ont reçu la moitié de la dose en infiltration sous-cutanée (sc) et le reste en infiltration péritonéale. Les niveaux de douleur ont été évalués avant l'intervention, puis 30 min., 12 et 24 h après l'intervention, d'après une échelle visuelle analogue. Le moment où a eu lieu la première analgésie et les besoins totaux d'analgésie pendant les 24 premières heures ont été enregistrés.

Résultats : Les patients qui ont reçu une combinaison d'infiltration sc et péritonéale de bupivacaïne ont présenté un niveau de douleur plus bas 30 min après l'intervention (32 ± 2 *vs* 54 ± 4; $P < 0,0001$), ont eu besoin d'une première analgésie plus tard que ceux de l'autre groupe (248 ± 20 *vs*164 ± 17 min; $P = 0,002$), d'une plus faible quantité d'opioïde (68 ± 5 *vs* 100 ± 7 mg; $P = 0,0002$) et d'analgésique non stéroïdien (65 ± 6 *vs* 96 ± 6 mg; $P = 0,007$) pendant les 24 premières heures postopératoires.

Conclusion : Une combinaison d'infiltration sc et péritonéale de bupivacaïne est supérieure à l'infiltration cutanée employée seule pour soulager la douleur ressentie après l'appendicectomie.

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ADEQUATE analgesia is important in patients undergoing abdominal surgery. Under treatment of post-operative pain is well documented.[1] Good post-operative analgesia is essential in maintaining respiratory function as well as facilitating early mobilization and discharge.[2] Opioids provide good pain relief particularly in severe pain. However, their use is restricted because of potential side effects.[3] Other analgesics including non-steroidal anti-inflammatory drugs are commonly combined with opioids.[4] The use of local anaesthetic agents may also avoid many of the potential problems associated with opioids.

The two most commonly used local anaesthetic preparations are lidocaine and bupivacaine. Subcutaneous lidocaine has been found to be effective by some for the relief of post-operative pain but results are conflicting.[5,6] The main disadvantage appears to be its short half life. Bupivacaine has a longer half life and has potential advantages for the relief of post-operative pain.[7] Administration of bupivacaine via skin infiltration, nerve block, extradural or spinal routes has been found to be effective.[8–10] Subcutaneous injection of bupivacaine after appendicectomy in children provides good early post-operative pain relief and a delay in the need for opioid injections post-operatively.[8]

The contribution of the peritoneum to pain experienced by patients presenting with appendicitis and following appendicectomy has not been considered in the literature. Indeed, the role of the parietal peritoneum in general has received little attention. Previous studies have examined post-operative analgesia following instillation of bupivacaine into the wound following herniorrhaphy and found a beneficial effect.[11–14] Intraperitoneal infiltration with bupivacaine has been used following laparoscopic cholecystectomy but the results are conflicting.[15–19] Alexander *et al.*[20] demonstrated benefit in pain scores at rest and following movement in patients receiving infiltration both of the parietal peritoneum and subcutaneous tissue compared with subcutaneous infiltration alone.

This study was established to examine the benefits of peritoneal analgesia in 60 patients undergoing appendicectomy. The patients were divided into two groups. In the first group, bupivacaine was given *sc* and in the second group half was given *sc* and half to the parietal peritoneum. The aim of the study was to compare the two routes of administration by assessing pain scores and further analgesic requirements in the first 24 hr after surgery.

Materials and methods

In this prospective double blind randomized study, following ethics committee approval, a consecutive series of 74 patients undergoing appendicectomy for suspected appendicitis were enrolled over six months. Informed consent was obtained from each patient. The patients were allocated to the study groups using a table of random numbers.

All patients received a standard anaesthetic and no premedication was given. The patients were pre-oxygenated with oxygen 100% for three minutes. The anaesthetic consisted of a rapid sequence induction with 5 $mg \cdot kg^{-1}$ thiopentone followed by 1 $mg \cdot kg^{-1}$ succinylcholine. While cricoid pressure was maintained, the tracheas were intubated and lungs ventilated to normocapnia using the Ohmeda 3 low flow circle system ventilator. Anaesthesia was maintained with oxygen 40%, nitrous oxide 60% and isoflurane titrated to clinical needs. Non-depolarizing neuromuscular blockade was maintained with 0.5 $mg \cdot kg^{-1}$ atracurium. Intraoperative analgesia consisted of 1 $\mu g \cdot kg^{-1}$ fentanyl and 0.1 - 0.2 $mg \cdot kg^{-1}$ morphine. A bolus dose of fentanyl was given at induction. An initial dose of 0.1 $mg \cdot kg^{-1}$ morphine was given. If the operation was prolonged, a further dose of 0.1 $mg \cdot kg^{-1}$ morphine was given to maintain arterial pressure and heart rate within 20% of baseline values. The total dose of morphine given was 0.1 - 0.2 $mg \cdot kg^{-1}$.

A standard post-operative analgesic regimen was utilized in all patients. The patient was prescribed 1 $mg \cdot kg^{-1}$ meperidine *im* given four hourly as required for analgesia. In addition, the patient was prescribed diclofenac, *pr* or *po*, (to a maximum of 2 $mg \cdot kg^{-1} \cdot 24\ hr^{-1}$).[20–21] Diclonefac *pr* was given every 18 hr and diclofenac *po* was given every eight hours. The maximum daily dose of diclofenac allowed was 150 mg in an average adult and the dose was reduced in children. The drugs were given on demand (within the limits defined above) by an experienced nurse with no knowledge of the route of local anaesthetic administration intra-operatively. The type of analgesia used was at the discretion of the nurse.

Surgery was performed using a standard appendicectomy incision. Patients with other pathology (14) were excluded from the study. These consisted of patients with ovarian cysts (10) or pelvic inflammatory disease (2). Two other patients proceeded to laparotomy, one for small bowel lymphoma and the second for perforated sigmoid diverticulum.

A dose of 1.5 $mg \cdot kg^{-1}$ bupivacaine 0.5 % (0.3 $mg \cdot kg^{-1}$) was used. The patients in group one received the entire dose of bupivacaine *sc*. Patients in group two received half the dose *sc* and half to the peritoneum. The peritoneum was held in haemostatic forceps and tented upwards. The dose of bupivacaine was calculated and half was drawn up into a syringe and given with a 23 gauge needle. The peritoneum was infiltrated under direct vision around the peritoneal

incision and a bleb was lifted at each site of injection. The subcutaneous injection was given after closure of the peritoneum in both groups.

Details were collected on all patients including name, medical records number, age, sex, weight and presentation as well as the white cell count and temperature at presentation. The incision type, length and the operative time were also recorded. The operative findings and the final histology were documented. Post-operative complications and days to discharge were recorded.

Pain intensity was scored from 0 (no pain) to 100 (worst possible pain) by means of a 100 mm visual analogue scale (VAS) which was recorded at rest. These were measured by an investigator without any knowledge of the analgesia given. Visual analogue scores were measured pre-operatively, 30 min, 12 hr and 24 hr post-operatively. Time to first analgesia was documented in either the post anaesthetic care unit or on the ward. Overall analgesic requirements within the first 24 hr were also recorded.

Statistical analysis was performed using the Levene test for homogenity of variance, unpaired Student's t test and the Chi square test with significance assumed at the 5% level.

Results

Seventy four patients were recruited but only 60 were eligible for analysis. There were 28 (47 %) patients in group one and 32 (53%) patients in group two. Both groups were equivalent with regard to age, sex, weight, white cell count and temperature pre-operatively, onset of pain and fasting time (Table I). There was no difference between the two groups with respect to length of incision, operative time, fentanyl or morphine use intra-operatively, operative findings or final histological diagnosis (Table I). One patient in each group had a wound infection post-operatively, one required drainage and one was managed conservatively.

There was no difference between the pain scores (VAS scores) in the two groups pre operatively. However differences were observed at 30 min ($P < 0.0001$) and 24 hr ($P = 0.03$). No difference was observed at 12 hr (Figure). The time to first analgesia was longer in patients in group two ($P < 0.002$). There was a difference in the cumulative dose of meperidine given during the first 24 hr ($P = 0.0002$), as well as the cumulative dose of diclofenac given during the first 24 hr ($P = 0.007$) between the two study groups (Table II).

Patients were divided on the basis of final histology into those with appendicitis and those without appendicitis and the two groups were compared. There was a difference in the leukocyte count but not in the temperature between the groups. There were no differences in VAS scores at any of the time period examined, no difference in time to first analgesia or in the cumulative dose of meperidine or other analgesics used in the first 24 hr post-operatively.

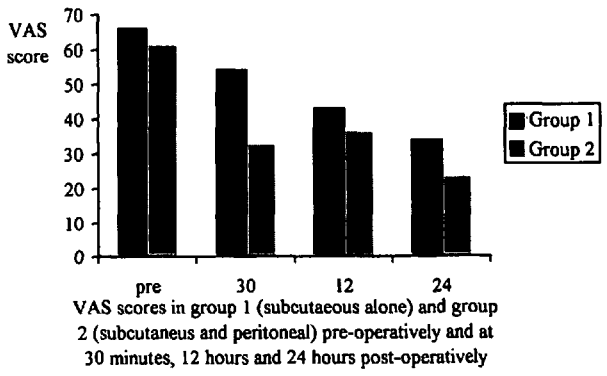

FIGURE VAS Score in group 1 and 2 patients

Discussion

Injection of local anaesthetic agents prior to, during or after appendicectomy has produced conflicting results.[6,8] Overall, these agents appear to provide some benefit in the relief of post-operative pain. Some of the studies examined the effects of lidocaine. One of the problems with lidocaine is its short half life. Bupivacaine has a longer duration of action which makes it a more suitable agent for post-operative pain relief.[7] It has been demonstrated that *sc* injection of bupivacaine after appendicectomy provides good early post-operative pain relief and delays the need for opioid injection.[8] Bupivacaine injection has also proved beneficial for post-operative pain relief when given *sc*, as a nerve block, extradurally or via the spinal route in many different operative procedures.[8-10]

A number of previous investigators have examined wound instillation with bupivacaine for the relief of post-operative pain. Casey *et al.*[17] compared instillation with ilioinguinal/iliohypogastric nerve block in children undergoing inguinal herniotomy and demonstrated no differences between these two techniques. Spittal[18] also found no difference between a field block and local anaesthetic instillation into wounds and Thomas *et al.*[16] and Shenfeld *et al.*[19] also found wound instillation to be of benefit. Similarly Sinclair *et al.*[15] found instillation with a lidocaine aerosol to be effective for the relief of post-operative pain. The present study found a benefit from peritoneal infiltration with bupivacaine.

There are very few studies reported that examined the benefits of peritoneal analgesia. In patients with

TABLE I Demographic features, presentation and operative findings in the two groups.

Variable	*Group I*	*Group II*	*Significance*
Number	28	32	
Sex (male)	34 (56.7 %)	26 (43.3 %)	NS
Age (yr)	23.2 ± 1.9	22.5 ± 1.6	NS
Weight (kg)	60.6 ± 2.3	63.9 ± 3.2	NS
Temperature (C)	37.1 ± 0.2	37.0 ± 0.1	NS
WCC × $10^9.l^{-1}$)	10.9 ± 0.8	10.1 ± 0.7	NS
Onset pain (hr)	32.1 ± 2.6	31.9 ± 2.5	NS
Arrival in Emergency Room (hr)	17.1 ± 1.8	18.4 ± 1.5	NS
Admission (hr)	14.6 ± 1.8	15.8 ± 1.5	NS
Decision to operate (hr)	11.3 ± 1.3	12.9 ± 1.5	NS
Length fasting (hr)	21.1 ± 1.8	22.3 ± 1.6	NS
length incision (cm)	4.2 ± 0.3	4.1 ± 0.3	NS
duration operation (min)	46.1 ± 3.0	51.2 ± 2.9	NS
morphine (intra-operatively) (mg)	8.2 ± 0.3	8.5 ± 0.4	NS
Histology - normal	8 (29 %)	13 (41 %)	
- inflamed	11 (39 %)	14 (44 %)	NS
- gangrenous/ perforated	9 (32 %)	5 (16 %)	
Days to discharge	3.7 ± 0.2	3.6 ± 0.2	NS

Mean ± SEM or as number (%).
NS = not significant. WCC* = white cell count.

TABLE II VAS scores and analgesic requirements in the two groups.

Variable	*Group I*	*Group II*	*Significance*
VAS 1 (Pre-operative)	66 ± 3 [59-73]	61 ± 3 [54-68]	NS
VAS 2 (30 min post)	54 ± 4 [46-62]	32 ± 2 [27-37]	< 0.0001
VAS 3 (12 hr post)	43 ± 4 [35-50]	36 ± 4 [28-45]	NS
VAS 4 (24 hr post)	34 ± 3 [27-41]	23 ± 3 [16-31]	0.03
Time to first analgesia (min)	164.4 ± 16.9 [129.7-199.3]	248.2 ± 20.2 [207.1-289.5]	0.002
Cumulative meperidine (first 24 hr) (mg)	100.3 ± 7.1 [85.6-115.1]	67.6 ± 4.5 [58.3-76.9]	0.0002
Cumulative diclofenac (first 24 hr) (mg)	95.5 ± 6.3 [82.6-108.5]	64.8 ± 5.8 [52.9-76.7]	0.007

Results given as mean (standard error of the mean) and [95 % confidence intervals of the mean]. VAS = visual analogue score;

appendicitis, peritoneal inflammation is a prominent feature at presentation. The contribution of peritoneal nerve fibres to the pain experienced by the patient post-operatively is unknown. In the present study, comparing peritoneal combined with *sc* delivery of local anaesthesia with *sc* delivery alone, beneficial effects were observed. The former group of patients had a better pain score at 30 min post-operatively, had a longer interval to first analgesia and had reduced opioid and non steroidal anti-inflammatory requirement in the first 24 hr post-operatively.

Intraperitoneal administration of bupivacaine has been examined following laparoscopic cholecystectomy and the results are conflicting.[23–25] Alexander *et al.*[20] examined administration of bupivacaine to the parietal peritoneum at the port sites following laparoscopic cholecystectomy combined with *sc* administration and compared this with *sc* administration alone. They found lower pain scores at 6 and 18 hr post-operatively, both at rest and following movement. In addition opioid and oral analgesic consumption were reduced but the results were significantly different. Similar results were observed in this study following appendicectomy.

Scheinin *et al.*[23] examined plasma bupivacaine concentrations following intraperitoneal administration in 60 patients undergoing elective laparoscopic cholecys-

tectomy. Plasma concentrations of bupivacaine peaked after 30 min and were below toxic levels. The dose of bupivacaine used was 150 mg in 100 ml bupivacaine 0.15%. In the present study 1.5 $mg \cdot kg^{-1}$ bupivacaine 0.5% was employed which is equivalent to 1 $mg \cdot kg^{-1}$ bupivacaine 0.15%. A recent study examining bolus delivery of 20 ml bupivacaine 0.5% by wound infiltration demonstrated plasma concentrations well below the toxic threshold and a slower increase to peak plasma concentrations than the peritoneal route.[26] The doses employed in this study were below those used by Scheinin *et al.*[23] and only half of the dose was given to the peritoneum. While the volume of solution given may appear large, the dose was well within the toxic limits of bupivacaine. In addition, bupivacaine has antimicrobial activity and may protect against wound infection.[11] No adverse effects on wound healing have been found in other studies.[12,14]

This method of delivery of local anaesthetic is easy, and no expertise or special training is required. It was not associated with any untoward side effect and did not interfere with the operative procedure. It appears to be a valuable adjunct to opioids and had an opioid sparing role. It provides a worthwhile supplementation to current methods of delivery of post-operative analgesia.

The present study was not established to examine the duration of action of bupivacaine for the relief of post-operative pain following appendicectomy. Most appendicectomies were performed late in the evening and it was considered unethical to awaken patients to measure pain scores. As a result, pain scores were measured at 30 min, 12 and 24 hr post-operatively. Bupivacaine has been shown to have an analgesic effect beyond the duration of its pharmacological action.[10] It has been postulated that bupivacaine suppresses the formation of a hyperexcitable state in the central nervous system which is responsible for the maintenance of post-operative pain.[19–20] In this study while differences were observed at 30 min and 24 hr, no differences were observed at 12 hr. However, the compounding effects of further analgesia are difficult to control. A difference was demonstrated for opioid and non steroidal anti-inflammatory usage in the first 24 hr post-operatively. This supports the contention that the clinical benefits of bupivacaine outlast its pharmacological duration of action.

In summary peritoneal combined with *sc* administration of bupivacaine has considerable advantages over *sc* administration alone. These include reduction in pain scores at 30 min post-operatively, increased interval to administration of additional analgesia and reduction in further analgesic requirements in the first 24 hr post-operatively. The use of this technique appears to provide a valuable adjunct to present methods of administering post-operative analgesia and it merits more widespread use.

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