PAIN MEDICINE
Volume 10 • Number 1 • 2009

The Effect of Preemptive Analgesia in Postoperative Pain Relief—A Prospective Double-Blind Randomized Study

Seetharaman Hariharan, MD, Harley Moseley, FFARCS, Areti Kumar, MD, and Senthilkumar Raju, MD

Department of Anaesthesia and Surgical Intensive Care, School of Clinical Medicine and Research, The University of the West Indies, Queen Elizabeth Hospital, Barbados

ABSTRACT

Objective. To analyze the effect of infiltration of local anesthetics on postoperative pain relief.

Design. Prospective randomized double-blind trial.

Setting. University Teaching Hospital in Barbados, West Indies.

Patients. Patients undergoing total abdominal hysterectomy.

Interventions. Patients were randomly allocated into one of four groups according to the wound infiltration: 1) preoperative and postoperative 0.9% saline; 2) preoperative saline and postoperative local anesthetic mixture (10 mL 2% lidocaine added to 10 mL 0.5% bupivacaine); 3) preoperative local anesthetic mixture and postoperative saline; and 4) preoperative and postoperative local anesthetic mixture. Both patients and investigators were blinded to the group allocation. All patients received pre-incision tenoxicam and morphine, standardized anesthesia, and postoperative morphine by patient-controlled analgesia.

Outcome measures. The amount of morphine used and the intensity of pain as measured by visual analog pain scale were recorded at 1, 2, 3, 4, 8, 12, 24, and 48 hours postoperatively.

Results. Eighty patients were studied with 20 in each group. Total dose of morphine used by patients who received preoperative and postoperative local anesthetic infiltration was lesser compared to other groups, although there was no statistically significant difference. Similarly, there was no difference in the intensity of pain between any groups.

Conclusions. Local anesthetic infiltration before and/or after abdominal hysterectomy does not reduce the intensity of postoperative pain and analgesic requirements.

Key Words. Preemptive Analgesia; Local Anesthetic Infiltration; Postoperative Pain

Introduction

Preemptive analgesia is the administration of an analgesic before a painful stimulus, such as tissue injury during surgery, in an attempt to obtain better pain relief compared with when the same analgesic intervention is used after the painful stimulus. The concept was propounded in the early 1980s when experimental studies showed that measures to antagonize the nociceptive signals before injury prevented central hypersensitization, thereby reducing the intensity of pain following the injury [1].

Clinical studies have conflicting results regarding the efficacy of preemptive analgesia. A meta-analysis published in 2002 showed that there is no conclusive clinical evidence to support preemptive analgesia [2]. However, a recent meta-analysis has shown that preemptive local anesthetic wound infiltration and nonsteroidal anti-inflammatory

Reprint requests to: Seetharaman Hariharan, MD, The University of the West Indies, Eric Williams Medical Sciences Complex, Mount Hope, Trinidad (West Indies). Tel/Fax: 868-662-4030; E-mail: uwi.hariharan@gmail.com.

 1526-2375/09/$15.00/49 49–53 doi:10.1111/j.1526-4637.2008.00547.x

drug (NSAID) administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores [3]. Potential reasons for the inability to clinically establish the efficacy of preemptive analgesia include differences in analgesic methods, the complex and multifactorial nature of pain, and the ethical constraints when studying pain in patients.

Although there have been a number of clinical trials to study the efficacy of preemptive analgesia, it is generally acknowledged that there are only a few randomized controlled double-blind trials in this clinical area of pain research [4]. There have been several clinical studies using either infiltration of local anesthetic drug or systemic analgesics [5–8]. However, to our knowledge, there has been no study using a mixture of local anesthetics for preoperative and postoperative wound infiltration and comparing their effect. With this background, the present study aimed to compare the effects of presurgical and postsurgical infiltration of a mixture of local anesthetic drugs on the intensity of postoperative pain and analgesic requirements.

Methods

Approval of the Hospital Ethics Committee was obtained prior to the study. Patients belonging to the American Society of Anesthesiologists (ASA)–Physical Status (PS) I and ASA–PS II, scheduled for abdominal hysterectomy were consecutively enrolled for the study. The objectives of the study, procedures involved, as well as the use of the patient control analgesia (PCA) pump and the visual analog scale (VAS) were explained to the patient prior to surgery, and informed consent was obtained from each patient. The patients were randomly assigned to one of the following groups: group A received preoperative and postoperative saline infiltration, group B received preoperative local anesthetic mixture and postoperative saline infiltration, group C received preoperative saline and postoperative local anesthetic mixture infiltration, and group D received preoperative and postoperative local anesthetic mixture infiltration. Saline infiltration comprised of 20 mL of 0.9% saline in a 20 mL syringe. Local anesthetic infiltration comprised of injection of a mixture of 10 mL of 2% lidocaine with 1:100,000 adrenaline and 10 mL of 0.5% bupivacaine taken in a single 20 mL syringe together, to make up the volume to 20 mL. The final concentration of the drugs would be 1% lidocaine and 0.25% bupivacaine and 2.5 μg/mL adrenaline. Drugs were drawn up by the scrub nurse prior to procedure in identical 20 mL syringes, in accordance with the random allocation of the patient to the specified group, and surgeons and anesthetists were blinded to contents.

The patients did not receive any benzodiazepine or opioid premedication. When they arrived at the waiting room, as soon as the intravenous fluids were started, all patients received tenoxicam (Tilcotil) 40 mg as infusion in 100 mL of the isotonic saline using a burette set. Intravenous fentanyl 1.5 μg/kg and midazolam 0.05 mg/kg were given 3 minutes before induction of anesthesia, and morphine 0.15 mg/kg was given prior to surgical incision. Anesthesia was induced with propofol 1–2 mg/kg, and endotracheal intubation was facilitated by *cis*-atracurium 0.15 mg/kg. The surgeons initially marked the line of incision with a marker. They were requested to administer the infiltration drugs along this line under the skin. Care was taken to ensure that the surgical incision was done along marked line after allowing at least 3 minutes for the drugs to act. Anesthesia was maintained by isoflurane in air/oxygen with low flows. Neuromuscular blockade was maintained with top-up doses of *cis*-atracurium.

At the end of the surgery, another intravenous cannula was placed and was dedicated to the use of PCA pump, and the pump was connected before the patient was fully awake. The PCA pump was set to deliver 1 mg morphine as a bolus when the patient activated with a lockout interval of 10 minutes. There was no background infusion of morphine. The surgeon was advised not to write any other analgesic prescription for the study patients. However, if rescue analgesia was needed, it was administered and recorded. The level of sedation was assessed using a 6-point Ramsay score, with scores >3 representing clinically significant sedation. The respiratory frequency was also recorded to avoid overdosage of opioids. A VAS score was used to quantify the pain during rest and not on movement (VAS 0 = no pain through 10 = excruciating pain). The total amount of morphine used in the PCA pump was recorded every hour for the first 4 hours, then every 4 hours for the first 24 hours, and 12 hourly for another 24 hours.

Results

A total of 80 patients were studied with 20 patients in each group. Forty-five patients (56.3%)

Table 1 Demographic data and surgery time

Group	Age (years) Mean (SD)	Weight (kg) Mean (SD)	Surgery time (hours) Mean (SD)
Saline–saline	44.8 (6.0)	74.8 (12.3)	1.57 (0.43)
Local–saline	43.6 (4.9)	79.4 (10.0)	1.61 (0.43)
Saline–local	44.5 (5.9)	72.9 (13.9)	1.73 (0.55)
Local–local	41.5 (5.5)	78.7 (10.0)	2.18 (2.2)

belonged to the ASA physical status I, and 35 (43.7%) belonged to ASA II category. The overall mean age of the patients was 43.6 years (5.7, standard deviation [SD]). The overall mean surgical time was 108 minutes (72, SD). Table 1 shows the demographic data and the surgical times within groups which were similar.

Fifty-nine patients continued to use morphine at the end of 36 hours which further decreased to 25 patients at the end of 48 hours. No patients required rescue analgesics. Table 2 shows the mean dose of morphine used (in milligrams) by patients in different groups at different time intervals. Although readings were recorded at many intervals, the readings at 1, 4, 12, and 24 hours postoperatively are shown in Table 2. Figure 1 shows the mean visual analog scores at different intervals, and although data were recorded at many intervals in the postoperative period, only the data during 1, 4, 12, and 24 hours are depicted in the figure. The levels of sedation and frequency of respiration were comparable in all the groups of patients, and no patient had any adverse clinical occurrence during the study.

A one-way analysis of variance, conducted to analyze the difference between the groups with respect to postoperative morphine consumption and pain intensity by VAS score, did not reach any statistical significance. A post hoc power analysis using statistical software showed that the power of the study was 72% at an α-level of 0.05 and an effect size of 0.25 [9].

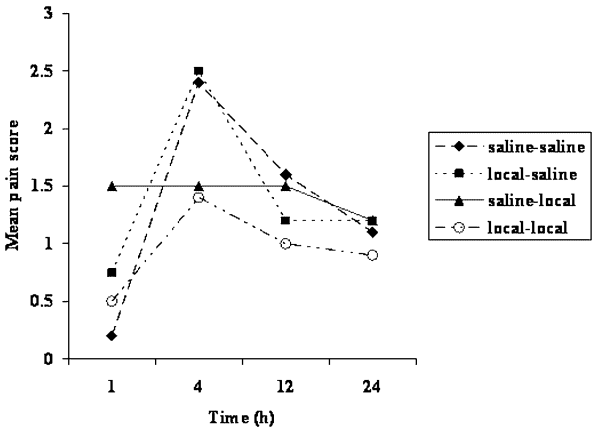

Figure 1 Mean visual analog pain scores at different time intervals.

Discussion

The salient finding of the present study is that preoperative and/or postoperative infiltration of the surgical wound with local anesthetics did not reduce the intensity of postoperative pain as well as analgesic requirements. Preemptive analgesia is an attractive concept of addressing pain even before it starts. Preemptive analgesia is known to prevent central sensitization of pain, thereby reducing hyperalgesia. There is experimental evidence from animal studies that tissue injury triggers neuronal changes and genetic expression of sensitization [10]. There is also the "wind-up" phenomenon which causes persistent spontaneous pain even in the absence of peripheral stimuli [11]. Hence, the primary goals of preemptive analgesia are to decrease acute pain following tissue injury, to prevent pathological modulation of the central nervous system (CNS) due to this pain, and to prevent development of chronic pain; clinical studies have been unable to clearly show the evidence for achieving these goals [12].

Ideally, the efficacy of preemptive analgesia can be clinically determined only if two similar groups of patients are compared. Pain relief should be compared in those who received preemptive analgesia with those who did not receive it, although all studies do not conform to this design [13]. The present study did have these two patient groups. When the efficacy of preemptive analgesia is studied, it is always assumed that the nociceptive

Table 2 Postoperative morphine usage (mg)

Group	Morphine 1 hour Mean (SD)	Morphine 4 hours Mean (SD)	Morphine 12 hours Mean (SD)	Morphine 24 hours Mean (SD)	Morphine Total Mean (SD)
Saline–saline	0.15 (0.5)	9.9 (6.3)	19.8 (10.4)	35.8 (17.2)	38.7 (19.9)
Local–saline	0.75 (1.4)	7.8 (5.5)	15.1 (7.9)	29.1 (9.9)	34.5 (12.2)
Saline–local	0.40 (1.1)	8.2 (4.5)	18.1 (7.6)	31.9 (11.4)	35.9 (11.3)
Local–local	0.70 (1.7)	6.7 (6.4)	13.5 (10.0)	24.4 (19.3)	29.3 (24.2)

barrage from the surgical incision primarily contributes to CNS sensitization. However, sensitization may not be necessarily limited by nociceptive inputs from the incision alone. It is unknown as to the relative contribution of other preoperative, intraoperative, and postoperative factors in this case such as the duration and degree of pathology in the condition being operated; psychological characteristics; and interoperative nociceptive, neuropathic, and visceral inputs contributing to sensitization. It may be assumed that intraoperative nociceptive inputs would be higher than that of the postoperative period. In this context, it has been suggested by many authors that the term "preventive analgesia" may be more apt than "preemptive analgesia" to describe the analgesia which covers the entire perioperative period [14–16]. Probably due to these issues, clinical benefits of preemptive analgesia have not been clearly identified because it may not be possible to completely block all possible pain signals originating from the surgical wound from the time of incision until final wound healing [17]. Our study similarly demonstrated no benefit.

Postoperative pain is usually quantified by the analgesic requirement and by using various pain scales, the most commonly the VAS, both of which were used in the present study. The requirement of analgesic is only an indirect measure of pain, and this can be confounded by patient factors such as pharmacokinetic and pharmacodynamic variations, varying pain thresholds, psychosocial makeup, and cultural influences [18]. The VAS measures only the pain-related behavior of the patient and can be equally influenced by all of these factors.

Usage of a mixture of bupivacaine and lidocaine has not been studied extensively. There are both disadvantages and advantages of this mixture. A study done as early as 1982 showed the beneficial effect of mixing bupivacaine and lidocaine for epidural anesthesia [19]. Lidocaine has a quicker onset of action, while bupivacaine continues to maintain the anesthetic action for a longer period. Also, pharmaceutically the mixture is compatible. There is also a theory that lidocaine affords a beneficial effect against the dysrhythmogenic potential of bupivacaine in the mixture [20]. The disadvantage may be additive toxicity because of the fourfold potential toxicity of bupivacaine compared to lidocaine. In the present study, because of the uniformity of the anthropometric variables as well as the surgical procedure, we had a fixed volume of the local anesthetic mixture, and none of the patients received these drugs near the toxic level. Also, there were no misadventures related to local anesthetics in the entire study.

Administration of systemic analgesics (opioids, NSAIDs, clonidine, etc.) is one of the modalities of preemptive analgesia studied [21–23]. All patients in the present study, irrespective of the group assignement, received systemic opioids and NSAIDs before surgery. Probably due to this treatment, the mean pain score was never above 3, and the maximum intensity of pain was during the period of 4 hours after surgery (Figure 1).

However, the present study did not compare the efficacy of systemic analgesics as a preventive analgesia and studied only the possible benefits of local anesthetic infiltration.

There are some limitations to the present study. The preoperative administration of potent systemic analgesics could have influenced the results. Differences such as preoperative pathology and duration, psychosocial characteristics, and intraoperative input were not controlled for. The sample size is small, although most of similar studies have only less than 20 patients in each group, and a previous meta-analysis included studies with 10 patients or more in each group [2]. Additionally, the post hoc power analysis found a reasonable power for the present study.

In conclusion, local anesthetic infiltration of the surgical wound preoperatively and/or postoperatively did not reduce the intensity of postoperative pain and analgesic requirements in patients undergoing abdominal hysterectomy. To adequately test the efficacy of this intervention, future studies will require larger samples to control for other characteristics, such as psychosocial factors, extent and duration of preoperative nociception, and intraoperative nociceptive input.

References

1 Woolf CJ. Evidence for a central component of postinjury pain hypersensitivity. Nature 1983;308: 386–8.
2 Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief—the role of timing of analgesia. Anesthesiology 2002;96:725–41.
3 Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: A meta-analysis. Anesth Analg 2005;100:757–73.
4 McQuay HJ. Pre-emptive analgesia: A systematic review of clinical studies. Ann Med 1995;27:249–56.

5 Dahl V, Raeder JC, Erno PE, Kovdal A. Preemptive effect of preincisional vs postincisional infiltration of local anaesthetic on children undergoing herniorplasty. Acta Anaesthesiol Scand 1996;40:847–51.
6 Hanlon DM, Colbert ST, Keane PW, Given FH. Preemptive bupivacaine offers no advantages to postoperative wound infiltration in analgesia for outpatient breast biopsy. Am J Surg 2000;180:29–32.
7 Gill P, Kiani S, Victoria BA, Atcheson R. Preemptive analgesia with local anesthetic for herniorrhaphy. Anaesthesia 2001;56:414–7.
8 Marc B, Istvan J, Donati F. Local anesthetic infiltration reduces opioid use after appendectomy. Can J Anaesth 2007;54(S–1):44352.
9 Power analysis for ANOVA designs. Available at: http://www.math.yorku.ca/SCS/Online_ (accessed June 10, 2007).
10 Todd AJ, Spike RC, Young S, Puskar Z. Fos induction in lamina I projection neurons in response to noxious thermal stimuli. Neuroscience 2005;131: 209–17.
11 Hughes AM, Rhodes J, Fisher G, Sellers M, Growcott JW. Assessment of the effect of dextromethorphan and ketamine on the acute nociceptive threshold and wind-up of the second pain response in healthy male volunteers. Br J Clin Pharmacol 2002;53:604–12.
12 Grape S, Tramèr MR. Do we need preemptive analgesia for the treatment of postoperative pain? Best Pract Res Clin Anaesthesiol 2007;21:51–63.
13 Kissin I. Preemptive analgesia at the crossroad. Anesth Analg 2005;100:754–6.
14 Kissin I. Preemptive analgesia: Terminology and clinical relevance. Anesth Analg 1994;79:809–10.
15 Katz J, McCartney CJ. Current status of preemptive analgesia. Curr Opin Anaesthesiol 2002;15:435–41.
16 Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. Curr Opin Anaesthesiol 2006; 19:551–5.
17 Dahl JB, Møiniche S. Pre-emptive analgesia. Br Med Bull 2004;71:13–27.
18 Kissin I. Preemptive analgesia: Why its effect is not always obvious. Anesthesiology 1996;84:1015–9.
19 Seow LT, Lips FJ, Cousins MJ, Mather LE. Lidocaine and bupivacaine mixtures for epidural blockade. Anesthesiology 1982;56:177–83.
20 de Jong RH. Local Anesthetics. St. Louis, MO: Mosby; 1994:354–5.
21 Yukawa Y, Kato F, Ito K, Terashima T, Horie Y. A prospective randomized study of preemptive analgesia for postoperative pain in the patients undergoing posterior lumbar interbody fusion: Continuous subcutaneous morphine, continuous epidural morphine, and diclofenac sodium. Spine 2005;30:2357–61.
22 Persec J, Persec Z, Bukovi D, et al. Effects of clonidine preemptive analgesia on acute postoperative pain in abdominal surgery. Coll Antropol 2007;31: 1071–5.
23 Reuben SS, Ekman EF. The effect of initiating a preventive multimodal analgesic regimen on long-term patient outcomes for outpatient anterior cruciate ligament reconstruction surgery. Anesth Analg 2007;105:228–32.