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A randomized, placebo controlled, trial of preoperative sustained release Betamethasone plus non-controlled intraoperative Ketorolac or Fentanyl on pain after diagnostic laparoscopy or laparoscopic tubal ligation [ISRCTN52633712]

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Abstract

Background: Gynecological laparoscopic surgery procedures are often complicated by postoperative pain resulting in an unpleasant experience for the patient, delayed discharge, and increased cost. Glucocorticosteroids have been suggested to reduce the severity and incidence of postoperative pain.

Methods: This study examines the efficacy of a sustained release betamethasone preparation to reduce postoperative pain and the requirement for pain relief drugs after either diagnostic laparoscopy or tubal ligation. Patients were recruited, as presenting, after obtaining informed consent. Prior to surgery, patients were randomly selected by a computer generated table to receive either pharmacy-coded betamethasone (12 mg IM Celestone™) or an optically identical placebo injection of Intralipid™ and isotonic saline mixture. The effect of non-controlled prophylactic intraoperative treatment with either fentanyl or ketorolac per surgeon's orders was also noted in this study. Blood samples taken at recovery and at discharge times were extracted and analyzed for circulating betamethasone. Visual analog scale data on pain was gathered at six post-recovery time points in a triple blind fashion and statistically compared. The postoperative requirement for pain relief drugs was also examined.

Results: Although the injection achieved a sustained therapeutic concentration, no beneficial effect of IM betamethasone on postoperative pain or reduction in pain relief drugs was observed during the postoperative period. Indeed, the mean combined pain scores during the 2 hour postoperative period, adjusted for postoperative opioids as the major confounding factor, were higher approaching statistical significance ($P = 0.056$) in the treatment group. Higher pain scores were also observed for the tubal ligation patients relative to diagnostic laparoscopy. Intraoperative fentanyl treatment did not significantly lower the average pain score during the 2 hour postoperative period. Intraoperative ketorolac treatment significantly lowered ($P = 0.027$) pain scores and reduced the postoperative requirement for additional pain relief drugs.

Conclusions: There was a lack of efficacy of preoperative sustained release betamethasone in reducing postoperative pain despite maintaining a therapeutic concentration during the postoperative period. Intraoperative Ketorolac did afford some short-term pain relief in the postoperative period and reduced the need for additional pain relief drugs.

Background

Laparoscopic procedures are often complicated by postoperative pain symptoms [1]. Manufactured derivatives of glucocorticoids such as betamethasone or dexamethasone are 25–30 fold more potent by weight than endogenous cortisol in terms of anti-inflammatory activity [2]. These compounds have been used to ameliorate postoperative pain symptoms in oral and laparoscopic surgeries [3,4] presumably by attenuation of lipid inflammatory mediators thought to have a role in postoperative pain [4]. More recently the effectiveness of glucocorticoids has been questioned in pediatric tonsillectomy [5], laparoscopic cholecystectomy [6] and inguinal herniorrhaphy with spinal anesthesia [7]. Celestone Soluspan is an injectable combination of fast acting and prolonged effect betamethasone. IM injection of 12 mg of Celestone has been reported to be efficacious in management of pain after ambulatory surgery, perhaps by delivering a longer lasting dose [4]. Since this prophylactic treatment is relatively safe and inexpensive, the current study was designed to test whether preoperative administration of this form of betamethasone would alleviate postoperative pain in women undergoing either tubal ligation or diagnostic laparoscopic procedures. In addition the intraoperative administration of either a prophylactic non-steroidal anti-inflammatory or an opioid per surgeons orders was evaluated along with the type of procedure.

Methods

Betamethasone was obtained from Schering-Plough Pharmaceuticals as an injectable 50% betamethasone disodium-phosphate (fast onset): 50% betamethasone acetate (slower onset and long acting) suspension (Celestone Soluspan™). Intralipid™, obtained from Kabivitrum Inc, is an aqueous suspension of lipid droplets that is sterile, suitable for intravenous feeding of patients and thus safe for IM injection [4]. Intralipid™ mixed with sterile isotonic saline was used to prepare a visually identical coded placebo injection prepared by the pharmacist. Pharmacy coded injections were provided to the anesthesiologist who along with the patient, surgeon and persons collecting postoperative data were blinded as to the contents.

Patients (N total of 74), as presenting, and after giving Institutional Review Board approved written informed consent conforming to the Helsinki II declaration, were randomly assigned by a computer generated table to betamethasone treatment (BM) or placebo (P) groups. Eight

patients were later excluded from further data collection when their surgery evolved from a laparoscopic into an open procedure, leaving a total of 66 patients evaluated for postoperative pain after either diagnostic laparoscopy (N = 37) or tubal ligation (N = 29). Prior to surgery, patients were assessed for preoperative pain. In this double blind and placebo controlled study the P group (N = 35) received a coded placebo injection of Intralipid™ mixed with sterile isotonic saline while the BM treatment group (N = 31) received a coded injection of 12 mg Celestone Soluspan™ IM (gluteal muscle) 30–60 minutes prior to surgery. Patients were pre-medicated with 2 mg versed and anesthesia was induced with 1.5 mg kg⁻¹ lidocaine, 3 mg curare, 2.5 µg kg⁻¹ fentanyl, 2.5 mg kg⁻¹ propofol, and 1.5 mg kg⁻¹ succinylcholine. Anesthesia was maintained with isoflurane in 65% nitrous oxide : 35 % oxygen, with muscle relaxation achieved with vecuronium if needed. Intraoperative analgesics, either an additional IV bolus of 2.5 µg kg⁻¹ fentanyl or 30 mg ketorolac (ketorolac trometamol) administered at the end of the procedure, were given to some of the patients per surgeon's instructions and noted as part of this study.

Pain was assessed using the position of the patient's mark on a 100 mm visual analog scale (VAS), with 0 = none and 100 = worst possible pain, at 15, 30, 60, and 120 minutes post operation. In all cases the interviewer was blinded as to the treatment. The type and amount of postoperative pain relief drugs from recovery till discharge was also noted.

Blood samples were taken by standard phlebotomy techniques upon recovery and at discharge. Serum samples were obtained by centrifugation and frozen at -70 °C until extraction and analysis by high performance liquid chromatography. Sera (0.5–1.0 ml) were twice extracted with 3 volumes of ether with collection of the ether phase. The solvent was evaporated at 40–45 °C under a gentle stream of nitrogen and the residue dissolved in 0.1 ml of water-acetonitrile (60:40, v/v, acidified to pH 3.45 with acetic acid) and centrifuged to remove insoluble material. Aliquots of 25 µL were analyzed on a Waters Symmetry-C18, 3.5 micron, 4.6 mm × 15 cm column using a Waters HPLC pump (Model 470) and WISP (Model 710B) autoinjector. Monitoring of the chromatograms was done with UV detection at 254 nanometers. Standards of betamethasone were run to establish calibration curves that were

used to convert peak areas from patient samples to nanograms ml⁻¹.

Two-sided statistical comparisons were done with StatView v4.5 (Abacus Concepts, Inc., CA, USA) computer program and SPSS version 10.0 (SPSS Inc., IL, USA). The groups were tested for differences using Student's unpaired and paired t-tests for continuous variables and Chi-Square for categorical variables. Repeated measures ANOVA with Huynh-Feldt correction was used to analyze multiple within-group comparisons, within subject effect of survey time, and the interaction between time and treatment. Regression analysis was used to determine the effect of the analgesics controlling for the other factors. All data were evaluated for normality of distribution, equality of variances, and other assumptions. If necessary, data were either log transformed to achieve a normal distribution or nonparametric tests were used. A *P* value of less than 0.05 was used to determine statistical significance.

Results

Eight patients, selected with the intention to treat, were excluded from the analysis when the laparoscopic procedure evolved into an open procedure. This resulted in a loss of 2 patients from the P group and 6 patients from the BM group. The remaining patient group characteristics are given in Table 1. The groups were well matched with respect to age, body mass index (BMI), surgery duration, time until recovery from anesthesia, and time until discharge from the hospital. The groups were also closely matched in the number of subjects classified as ASA II health status (54% P group, 45% in the BM group), postmenopausal status (11% P group, 16% BM group), and subjects experiencing preoperative pain (26% P group, 29% BM group). The number of tubal ligations and diagnostic laparoscopy procedure were also evenly distributed between groups (48% tubal ligation in the BM group and 40% in the P group). Extra analgesics administered at the end of the surgery, per surgeon's orders, consisted of ketorolac (8 in the P group, 9 in the BM group) or fentanyl (10 in the P group, 8 in the BM group).

As shown in Figure 1, pain scores for the BM treatment group were higher at all postoperative time points and reached statistical significance (*P* < 0.05, power > 0.8) by repeated measures ANOVA at the 60 and 120 minutes survey times. To determine that this formulation of betamethasone given IM achieved a sustained circulating concentration, we sampled blood at recovery and upon discharge and analyzed every other patient sample in the BM treatment group. A stable serum concentration was obtained with no significant difference in betamethasone concentrations (*P* = 0.95 by paired t-testing) between the recovery (70 ± 12 nanograms ml⁻¹ mean ± S.E.M.) and discharge (71 ± 8 nanograms ml⁻¹) sera from the same

patient. There was also no significant difference in mean betamethasone concentrations between obese and normal weight patients in this group at either time point. This data were also evaluated by examining the influence of weight. There was no significant Spearman Rank correlation between the patient's weight and betamethasone concentrations at either sampling time (*P* = 0.59 at recovery, *P* = 0.25 at discharge).

Although not a controlled part of this study, fentanyl or ketorolac were given at the end of the intraoperative time for a considerable number of patients in the study. The effect of these treatments was also evaluated independently of the betamethasone treatment (which had no significant effect on the other treatments, *P* values all > 0.05). The treatment with fentanyl had no significant effect (*P* values all > 0.05) on pain at any of the time points with the greatest difference observed at 120 minutes after surgery (fentanyl pain VAS 19 ± 4, versus 29 ± 4, mean ± S.E.M., *P* = 0.15). Shown in figure 2, are the pain scores for the ketorolac treated patients, compared to the rest, without regard for betamethasone treatment. Ketorolac did significantly lower pain scores at the 15 minute survey time and pain scores were lower through the 60 minute postoperative time but not at later time points. Also significantly correlated (*P* = 0.016) was a lower requirement (76% versus 96%) for additional pain drugs in the recovery to discharge period, which was not observed for the intraoperative fentanyl treatment (94% versus 90%, *P* = 0.54). However, ketorolac did not significantly shorten the time from recovery to discharge (treated 178 ± 10, other 192 ± 11, mean minutes ± S.E.M., *P* = 0.49).

The type of surgery was associated with a significant difference in preoperative pain (slightly greater for the diagnostic laparoscopy group, *P* = 0.023) and in postoperative pain experienced at 60 minutes after surgery (greater for the tubal ligation group, *P* = 0.018) as shown in Figure 3. The average surgery time for tubal ligation was not significantly shorter (73.9 ± 9.3 versus diagnostic laparoscopy 96.8 ± 8.0 minutes ± S.E.M., *P* = 0.07, unpaired T-Test). Recovery times and time to discharge were also similar and not significant (*P* > 0.34). Tubal ligation was associated with higher pain levels through the discharge time point and was not reduced by betamethasone or by intraoperative fentanyl. Ketorolac did provide significant pain relief at 15 minutes after either tubal ligation surgery (*P* = 0.028) or diagnostic laparoscopy (*P* = 0.024), but not at later time points.

Only 6 patients did not require additional pain drugs in the postoperative period until discharge and significantly (Fisher Exact Test *P* = 0.026) all of these were in the placebo group. In the first 1 hour time period 80% of the patients received at least one dose of an opioid (48% - 25

Table 1: Patient Characteristics

Parameter	Group P (N = 35) BM (N = 31)	Median	Minimum	Maximum	Variance
Age (years)	P	29	21	49	65
	BM	30	21	46	44
BMI (kg m ⁻²)	P	28.6	19.8	39.1	25.9
	BM	27.0	19.3	45.0	38.0
Surgery time (minutes)	P	67	38	214	2891
	BM	75	32	291	2196
Recovery time (minutes)	P	81	37	215	1305
	BM	97	38	222	1385
To discharge time (minutes)	P	168	114	347	3195
	BM	175	108	438	6361

µg fentanyl IV, 21% – 2 mg morphine IV, 5% – 12.5 mg Demerol IV, 1 patient – 0.6 mg Dilaudid IV, 23% – 1 tablet Percocet PO) for pain relief. A single dose of 30 mg ketorolac was also given to 17 patients, 2 also receiving intraoperative ketorolac. For statistical analysis the total doses of pain medications were summed for the entire recovery to discharge time period. The number of doses, normally distributed with a only slight positive skewness, had a mean of 5.2 ± 0.4 S.E.M. and a median number of 5 doses of pain medications (range of 0–17 doses).

Regression analysis was used to study which factors influenced the mean of the postoperative pain scores during the first two hours. The measures included preoperative pain, betamethasone treatment, intraoperative ketorolac, and the number of opioid doses. Two-way interactions of those factors were also examined to verify that the different groups had equal slopes between the covariates and postoperative pain. Preoperative pain, which had potential as a covariate, showed no relationship with postoperative pain since the great majority of subjects had no preoperative pain. The most significant factor was number of postoperative opioid doses ($P < 0.001$), followed by intraoperative ketorolac treatment ($P < 0.025$), see Table 2. After correcting for the postoperative opioid doses and intraoperative ketorolac administration, the effect of betamethasone treatment was not quite significant at $P = 0.056$. These combined factors were able to account for 39% of the variance in the post-operative pain scores.

Discussion

This study indicates that the betamethasone, Celestone Soluspan, administered IM is not an effective treatment for gynecological laparoscopic postoperative pain. Indeed, higher pain scores were reported in the postoperative time period by the BM treatment group. One possi-

ble mechanism for this increase might be a reduction in plasma beta-endorphins which might increase pain perception. This has been reported after surgical extraction of impacted teeth in subjects pretreated with a closely related glucocorticoid, dexamethasone [8]. In contrast to our results, a previous study [4] reported that 12 mg slow and fast acting IM betamethasone significantly reduced postoperative pain by 50% in patients undergoing ambulatory hemorrhoidectomy or hallux valgus correction surgery. These significant beneficial effects were not observed at the 1 hour postoperative time point, but were observed at 2, 3, and 4 hours. In our study the median postoperative time to discharge was 166 minutes (P) and 177 minutes (BM). This suggests that the type of procedure and duration of recovery time may be important considerations for Celestone Soluspan's therapeutic results. The average body mass index in the previous study using Celestone Soluspan at 12 mg IM (BMI = 23 ± 6 Std. Dev.) in a Norwegian population [4] was lower than the BMI = 27 ± 6 for the American treatment group in this study. We analyzed the data to determine if greater BMI or weight may reduce the systemic circulating concentration of betamethasone, but found no significant difference between obese and normal weight groups. The mean circulating serum concentration for betamethasone determined in this study was 70 at recovery and 71 nanograms ml⁻¹ at discharge, an average of 3 hours later. This is comparable to the 83 – 115 nanograms ml⁻¹ peak plasma concentration at 10 – 36 minutes with a clearance half time of 5 – 6 hours after a therapeutic IV dose of 10.6 mg [9].

We also evaluated prophylactic intraoperative administration of either fentanyl or ketorolac administered per surgeon's orders. In agreement with previous studies [10,11] we found ketorolac did provide short-term pain relief in the postoperative period up to 120 minutes and signifi-

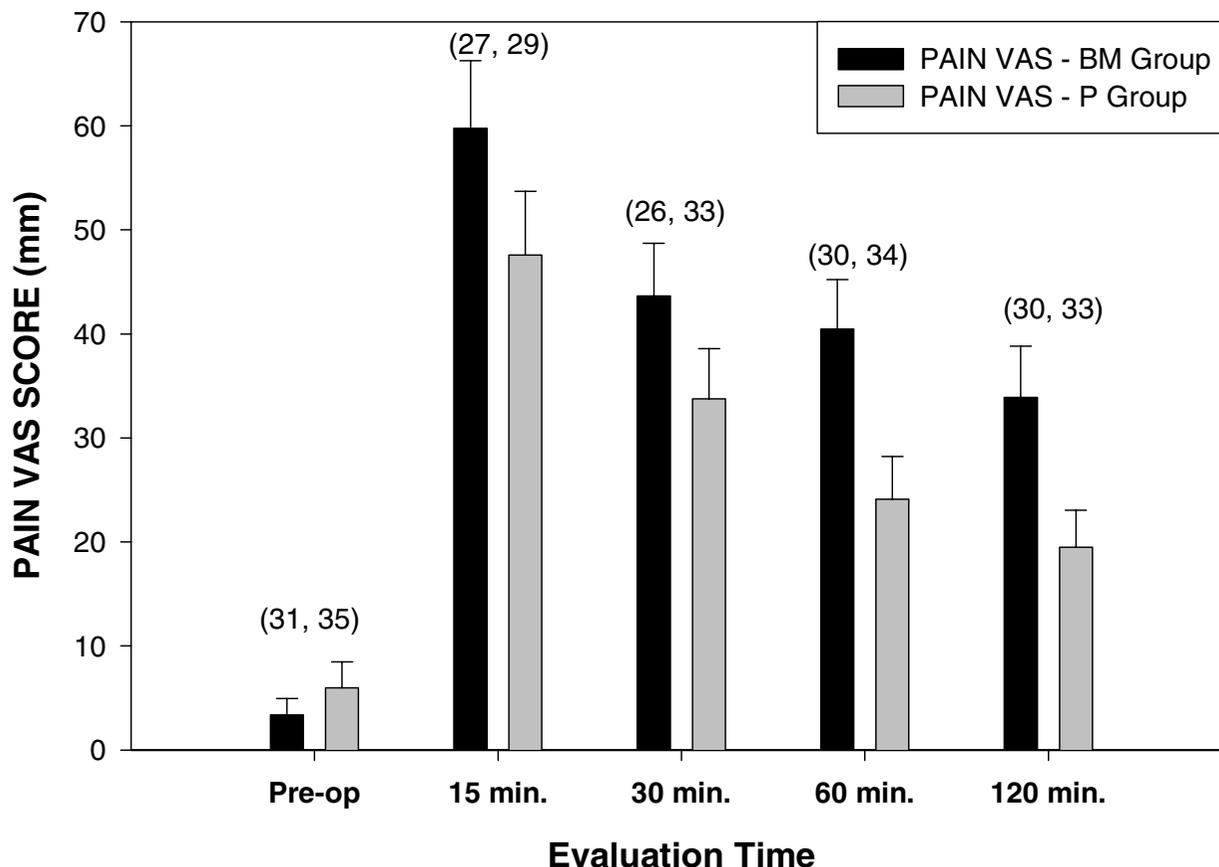


Figure 1

Plotted are the mean (+ S.E.M. error bar) visual analog scores (VAS) for pain using a patient-marked 100 mm line with 0 = no pain and 100 = worst pain. Repeated measures ANOVA as indicated for the P group (shaded bar) and BM group (solid bar). Number of subjects interviewed at each time point is indicated above each set of bars. Number lower than enrolled reflects unresponsive subjects at early postoperative times and subjects discharged early for later time points. Repeated measures ANOVA showed a significant within subject effect of time ($F = 7.9921$ (with Huynh-Feldt correction) ; $P = 0.02$) but the interaction between time and treatment were not significant ($F = 0.453$; $P = 0.84$).

cantly reduced the need for postoperative pain relief drugs. However, we did not find the reported [10] difference in effectiveness of ketorolac between diagnostic laparoscopy and tubal ligation. Prophylactic intraoperative fentanyl had no significant effect on postoperative pain scores or drug requirements. However, a major confounding factor in this study is the prevalence of opioid doses given in the 2 hour postoperative period which has a highly significant effect on the average pain scores.

The type of surgery and timing of preemptive analgesia for postoperative pain has recently been reviewed as a literature analysis [12] with the conclusion that current approaches are ineffective and more aggressive preemptive treatments are indicated. The definition of a clinically significant reduction in pain was also addressed in this review. Pain scores on a 0–100 mm VAS were associated with a verbal rating of no (0), light (25), moderate (50) and severe (75). Studies with control group postoperative scores < 30 mm were considered less significant since a preemptive treatment reduction would be difficult

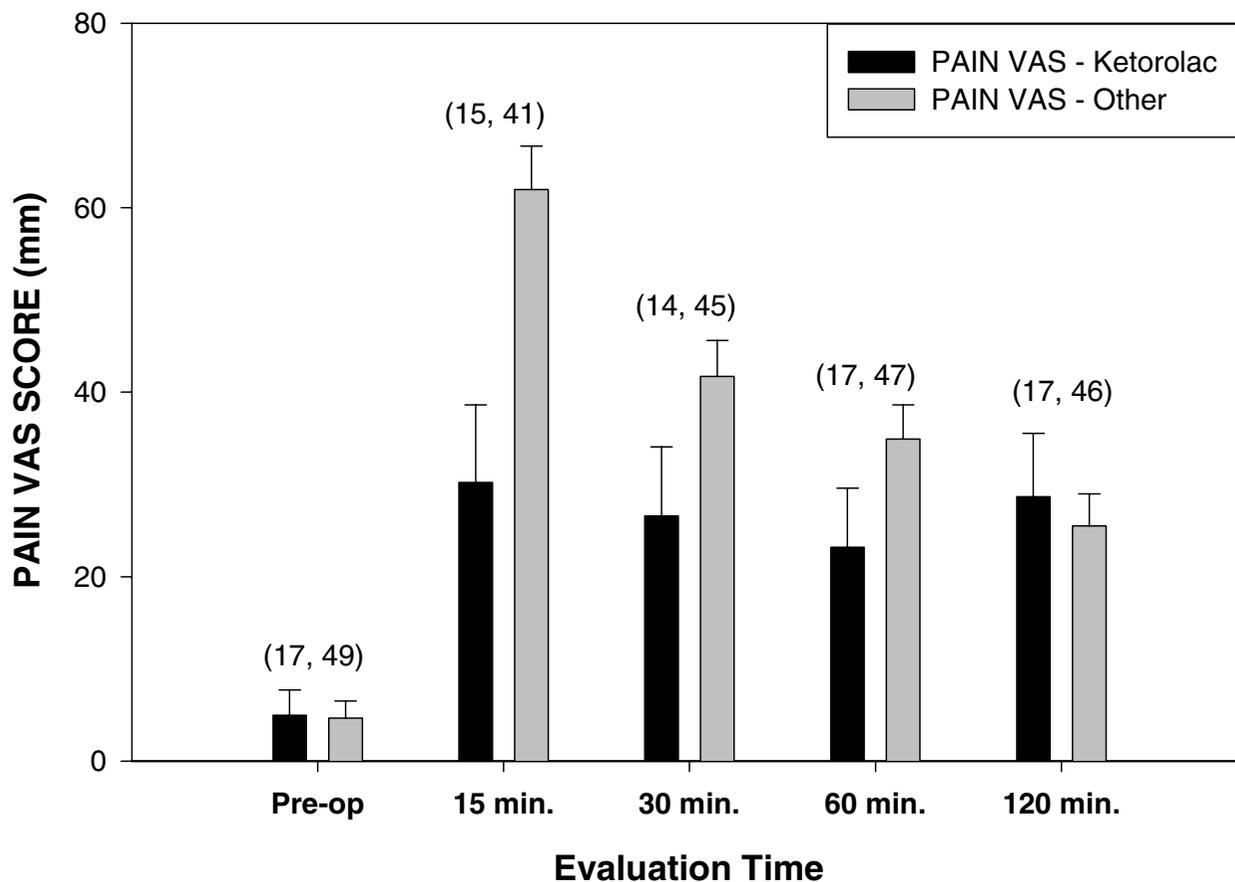


Figure 2

Plotted are the mean pain VAS scores (+ S.E.M. error bar) at survey times as in Figure 1. Repeated measures ANOVA as indicated for all the other patients (shaded bar) compared to the patients with intraoperative prophylactic treatment with Ketorolac (solid bar). Number of subjects interviewed at each time point is indicated above each set of bars. Number lower than enrolled reflects unresponsive subjects at early postoperative times and subjects discharged early for later time points.

Repeated measures ANOVA showed a significant, within subject, effect of time ($F = 13.776$ (with Huynh-Feldt correction) ; $P = 0.009$) but the interaction between time and treatment approached significance ($F = 2.150$; $P = 0.06$).

to detect. In this study, immediate postoperative pain scores were generally in the moderate range (50–75) with only intra-operative ketorolac reducing pain in the first 15 minutes to the light range (25–50).

Conclusions

Despite achieving a sustained therapeutic plasma concentration of betamethasone, pain perception was significantly increased in the immediate postoperative period for the patients treated preoperatively with Celestone Soluspan IM relative to placebo treated control

subjects in this triple blind randomized study. These results indicate that anti-inflammatory steroids may be useful in certain procedures, but are not uniformly effective in laparoscopic procedures with different patient populations. Although not a controlled part of this study, the confounding variables of extra intraoperative analgesics, type of laparoscopic operation, and postoperative analgesics were also evaluated for impact on average postoperative pain. The most significant effect was postoperative opioid dose. Intraoperative administration of ketorolac significantly reduced early pain scores and the

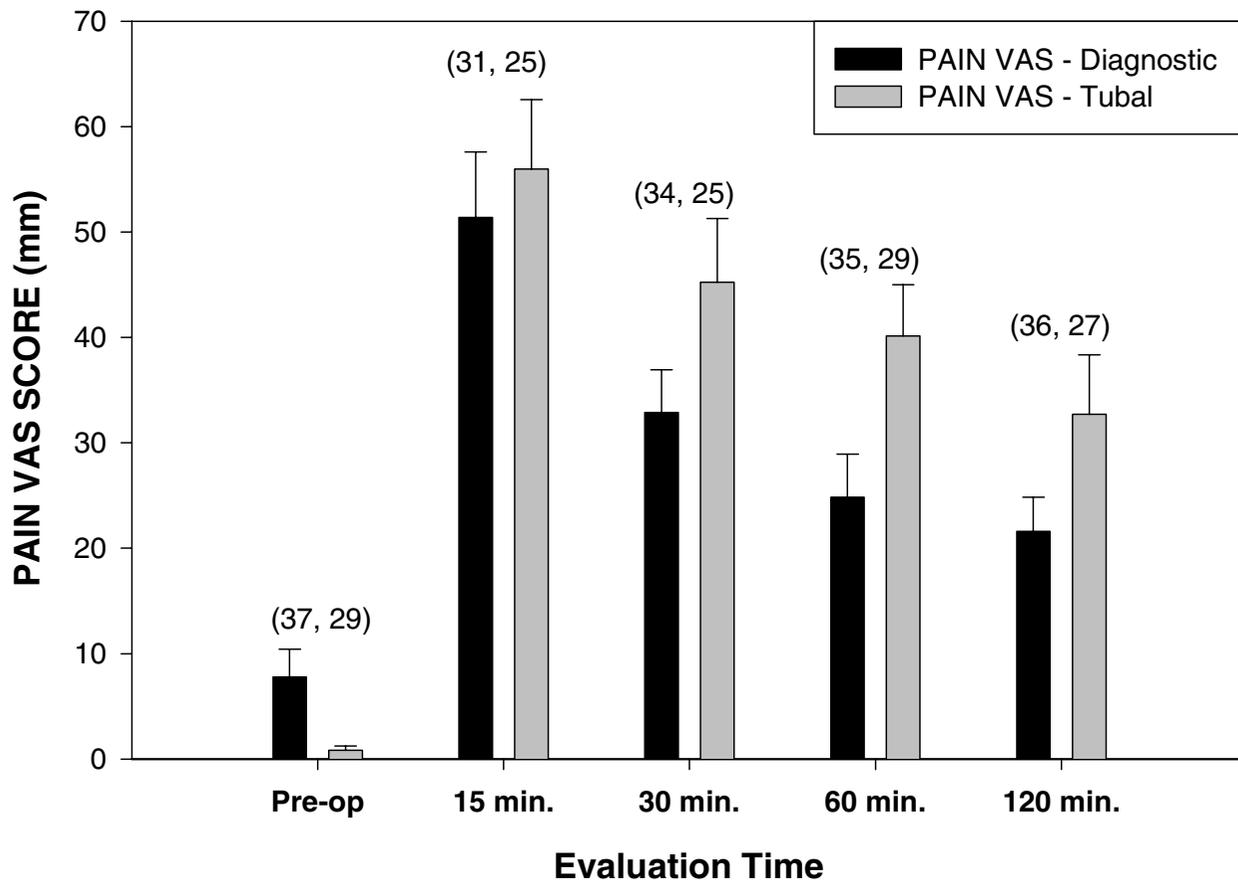


Figure 3

Plotted are the mean pain VAS scores (+ S.E.M. error bar) with survey times as in Figure 1. Repeated measures ANOVA as indicated for patients undergoing tubal ligation (shaded bar) compared to the patients having diagnostic laparoscopy (solid bar). Number of subjects interviewed at each time point is indicated above each set of bars. Number lower than enrolled reflects unresponsive subjects at early postoperative times and subjects discharged early for later time points. Repeated measures ANOVA showed a significant, within subject, effect of time ($F = 20.096$ (with Huynh-Feldt correction) ; $P = 0.009$) but interaction between time and treatment were not significant ($F = 1.086$; $P = 0.37$).

Table 2: Test Of Treatment Effects On Average Pain During The 2 Hour Postoperative Period

Treatment Pairs	Adjusted Means	Standard Error	95% Confidence Interval	Partial P Value
P (N = 35)	30	4	23 – 38	0.056
BM (N = 31)	40	4	33 – 47	
Ketorolac (N = 17)	29	5	20 – 38	0.027
Other (N = 49)	41	3	36 – 47	
Diagnostic (N = 29)	32	3	26 – 39	0.275
Tubal (N = 37)	38	4	30 – 46	

Means are adjusted by an average opioid dose of 2.9 during the 2 hour postoperative period.

requirement for postoperative pain relief drugs. Extra intraoperative fentanyl was associated with an insignificant reduction, both in pain scores at the 2 hour time point and in postoperative pain relief drugs.

Competing Interests

None declared.

Author's Contributions

WB conceived the study. WB, AS, and JH, initially designed the study, recruited, and treated the patients. CS and JH conducted patient pain scoring as well as collecting and processing blood samples. GS and CS were responsible for extracting serum samples and carrying out HPLC analysis. MP, PC, and RC carried out the statistical analysis and interpretation. WB and RC primarily drafted the manuscript. All authors read and approved the final manuscript.

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