

The Effect of Dexamethasone on Post-operative Opioid Requirement in Patients who Underwent Gynecology Surgery at the University Hospital in Jamaica

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Abstract

Background: The necessity to improve post-operative analgesia and hence patients' satisfaction has been the driving force of the quest for easy-to-administer, cost effective and safe analgesic agents. Dexamethasone is a powerful anti-inflammatory, analgesic and anti-emetic agent, that has been found to decrease opioid use, yet improve post-operative analgesia in a wide range of surgical patients.

Objectives: To determine if a single dose of intravenous Dexamethasone (0.5 mg/kg, not exceeding 40 mg), administered preoperatively, decreased post-operative opioid requirements without adverse effects in a cohort of Jamaican patients.

Study design: A randomized, single-centre, single-blinded study was conducted over a six (6) month period. Patients, 18-60 years, scheduled to undergo gynecological surgery under general anesthesia, were recruited for the study, and were enrolled in either Group A, the control or B, the study group. Anesthesia was standardized and included intravenous Morphine (0.1 mg/kg) and Diclofenac sodium 75 mg, for preemptive analgesia. Pain intensity, sedation level, post-operative opioid/narcotic usage and satisfaction with pain management were assessed at 3, 6, 9 and 12 hours post-operatively.

Results: Total Pethidine consumption for the control group (A) was significantly higher (5200 mg) than the study Group (B), 3800 mg ($p=0.008$). Age of patients and length of surgery were not found to influence Pethidine requirements ($p=0.338$ and 0.131 respectively). Pain intensity was significantly lower in Group B at the 12-hour assessment, $p=0.019$, and earlier discharge home was also noted. No adverse effects of Dexamethasone were observed.

Conclusion: A single intravenous dose of Dexamethasone had a positive effect on post-operative pain management and patient satisfaction in a cohort of Jamaican patients.

Keywords: Dexamethasone; Post-operative pain; Gynecological surgery

Introduction

The literature is laden with studies that indicate that post-surgical pain is still poorly managed [1,2]. At the University Hospital of the West Indies (UHWI), several limitations are believed to hamper adequate management of post-operative pain. These include: (i) fear amongst medical and nursing staff regarding the side effects of opioids, resulting in some patients being under-dosed; (ii) lack of routine objective pain assessment; (iii) limited availability of a wide range of analgesic agents; (iv) lack of patient-controlled analgesia (PCA) infusion pumps; (v) inadequate nursing staff on the surgical wards causing delays in analgesia administration and (vi) the lack of specific nurses trained in the identification and management of complications of analgesic agents. Poorly managed post-operative pain is associated with various organ-systems changes which negatively impact post-operative recovery, and can increase morbidity, mortality, hospital stay and health cost [3-6].

Tremendous advancement in the management of post-operative pain has been made in the past decades. The multimodal approach has become the norm, involving the use of various classes of analgesic agents. Class-specific undesirable side effects may be reduced with this approach due to lower dosing in each medication class, and synergism is likely to increase the analgesic efficacy. Analgesia groups include; opioids, non-steroidal anti-inflammatory drugs (NSAIDS),

local anesthetic agents, N-methyl-D aspartic acid (NMDA) receptor antagonists (e.g. Ketamine), magnesium, steroids (particularly Dexamethasone), Acetaminophen (Paracetamol), as well as non-pharmacologic techniques. Several studies have shown that steroids, particular Dexamethasone administered in various doses, intravenously (IV) or intra-theccally, reduced; pain intensity, Morphine/Pethidine consumption, nausea and vomiting (PONV) post-operatively [7-13].

The overarching aim for the conduct of this study, is to improve post-operative analgesia and hence patients' satisfaction. Dexamethasone, a powerful anti-inflammatory, analgesic and anti-emetic agent, was chosen as the study drug because it is readily available, easy-to-administer (requiring no special delivery device), and has been deemed

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to be safe as an adjunct for post-operative analgesia by several studies. Such studies have shown that it decreases opioid use, and improve post-operative analgesia in a wide range of surgical patients [7-13]. The effects of Dexamethasone was studied in a cohort of patients at the University Hospital of the West Indies undergoing tonsillectomy, and was deemed to be efficacious with no side effects [12], hence the interest in another cohort of patients. The authors therefore hypothesized that: (i) patients who received Dexamethasone, would have significantly less opioid consumption post-operatively; (ii) would have good analgesia such that the VAS and VRS scores would be significantly reduced and (iii) that there would be no associated side effects.

Subjects and Methods

Approval for the study was obtained from the University of the West Indies and the University Hospital of the West Indies (UWI/UHWI) Ethics Committee. The sample size of 80 patients was generated using the Raosoft sample size calculator using a prevalence of 50%, confidence interval of 95% and a margin of error of 5%. Patients, 18-60 years, ASA I and II scheduled to undergo gynecological surgery at the UHWI under general anesthesia, during the six (6) month period, were the targeted study population. On the day prior to surgery, after the pre-operative anesthetic assessment, the patients were informed, recruited and consented for participation in the study. Each patient picked a sealed envelope from a box and was enrolled in either Group A or B. Patients in Group A (n=40) served as the control and those in Group B (n=40) were given intravenous Dexamethasone (0.5 mg/kg, not exceeding 40 mg) 5 minutes post induction of anesthesia and before surgical incision. Anesthesia was standardized using; Propofol 1.5-2.5 mg/kg and Cisatracurium 0.15-0.2 mg/kg, the latter to facilitate endotracheal intubation and positive pressure ventilation. Preemptive analgesia was provided at induction, with Morphine 0.1 mg/kg and Diclofenac sodium 75 mg. Maintenance of anesthesia was with Isoflurane (0.6-1.2 volume percent) and a 50% mixture of oxygen and nitrous oxide. Patients were followed for 12 hours post-operatively by blinded trained medical personnel, and were assessed at 3, 6, 9 and 12 hours post-operatively. Pain intensity at rest and with movement was assessed using the visual analogue and verbal rating scales (VAS and VRS). The simplified sedation scale was used to assess sedation level. Opioid/narcotic administration was determined from the medication chart (MC) and satisfaction with pain management was via the verbal response scale {VReS} [14,15].

In the Post Anesthesia care Unit (PACU), patients received intravenous Morphine as needed, at a dose of 0.05-0.1 mg/kg based on clinical parameters and objectively, using the VAS and VRS. Analgesia on the Gynecological ward was ordered by the surgical team. In all cases, the order was 100 mg Pethidine six hourly intramuscular as needed.

Post-operative pain intensity was scored using the 10 cm visual analog scale (VAS), (0=no pain, to 10=worse pain experienced). Pain intensity at rest and with movement (turning in bed) was assessed using the VRS of 0-3 (none, mild, moderate, severe). The level of sedation was scored as 0-3 (alert, mildly drowsy, moderately drowsy, asleep). Nausea, vomiting, vital signs (pulse rate, blood pressure and respiratory rate) and adverse events along with intervention were recorded.

At the end of the 12-hour assessment period, patients were asked to make a global rating of their satisfaction with their post-operative pain management and document same on the verbal response (VReS) patients' form. The scores ranged from 0-4, corresponding to poor, fair, good, very good and excellent satisfaction.

The anesthetic staff was informed (verbally and via a printed leaflet) of the study, and were instructed regarding the conduct of anesthesia and to only administer Dexamethasone to patients in group B. The envelope which the patients picked from a box was taped to their docket. None of the two main investigators were involved in the anesthetic management of the patients, and remained blinded when they did the post-operative assessment.

Statistical Analysis

The data was entered into the Statistical Package for the Social Sciences (SPSS) software version 16. The primary outcome variable was the total amount of supplemental pethidine required over the 12-hour study period. Simple frequency tables of all variables were generated. In order to summarize the variables relating to pain intensity and opioid consumption at each assessment stage, means median and standard deviation were calculated, to which descriptive evaluations were then assigned.

The variables assessed were: age of patient, blood loss, length and type of surgery versus patient group. Bi-variate analysis involved cross-tabulations to determine if any trend existed between pairs of variables. Simultaneously, the 2-Way Chi-square non-parametric test was performed on data pairs to determine if a statistical significant relationship existed. A p-value of less than or equal to 0.05, indicated a statistically significant relationship. Phi & Cramer's V values were also determined in order to deduce the strength of the relationships [16].

Results

During the study period, 157 women who were scheduled to undergo elective gynecological surgery, were screened for eligibility to be enrolled in the study, of which 83 (53%) were eligible and were consented to participate. Seventy four patients did not meet the inclusion criteria based on; age over 60 years, American Society of Anesthesiologists (ASA) score of III and higher due to multiple comorbidities, chronic pain syndrome, long term use of steroid, cocaine and cannabis use. Three patients were de-recruited; two due to massive intra-operative haemorrhage and prolonged recovery room stay, and one due to post-operative intensive care admission.

Forty (50%) patients served as the control (Group A) and 40 (Group B) received Dexamethasone. All the patients were black Afro-Jamaican, and all underwent general anesthesia. The mean age and standard deviation for Groups A and B patients were: (41+9) and (41+7) years respectively. There was no significant statistical difference between the groups (p=1.0). The average weights of patients in Group A was (83.2+7) and (82.3+8 Kg) for Group B's patients (p=0.55). Total abdominal hysterectomy (TAH) was the commonest procedure performed, 49 or 61%. Myomectomy, the second most common procedure was done for eighteen (22.5%) patients (Table 1).

Thirty (75%) patients received 40 mg Dexamethasone, nine (22.5%) received between 30 and 39 mg, and one patient received the minimum dose of 28 mg. The mode was 40 mg, but a kurtosis of 14.938 and a standard error of kurtosis of 0.532 were calculated, in keeping with the significantly skewed dosage pattern.

The mean length of surgery and standard deviation (SD) were (102+38 minutes) for Group A and (101+51 minutes) for group B. This did not achieve statistical significance; p=1.00. The mean length of stay in the PACU for Groups A and B were; (123+68 minute) and (126+75) respectively. This too, showed no statistical significant difference between the two groups; p=0.264. The mean blood loss for Groups A

Surgical procedure	Frequency Gp A (%)	Frequency Gp B (%)	Total
Total Abdominal Hysterectomy	22 (55.0%)	27 (67.5%)	49 (61.25%)
Myomectomy	11 (27.5%)	7 (17.5%)	18 (22.5%)
Adhesiolysis	1 (2.5%)	1 (2.5%)	2 (2.5%)
Manchester repair for Uterine prolapsed	1 (2.5%)	1 (2.5%)	2 (2.5%)
Ovarian cystectomy	1 (2.5%)	1 (2.5%)	2 (2.5%)
Tubuloplasty	2 (5.0%)	0 (0%)	2 (2.5%)
Left oophorectomy	0 (0%)	1 (2.5%)	1 (1.25%)
Salpingectomy	0 (0%)	1 (2.5%)	1 (1.25%)
Subtotal hysterectomy	1 (2.5%)	0 (0%)	1 (1.25%)
Vaginal myomectomy	1 (2.5%)	0 (0%)	1 (1.25%)
Wedge resection of Left ovary	0 (0%)	1 (2.5%)	1 (1.25%)
Total	40 (100%)	40 (100%)	80 (100%)

Table 1: Types and frequency of surgical procedures performed.

and B were (521+322) and (647+441) milliliters (mls.). This did not meet statistical significance, $p=0.256$. Blood loss exceeding 1000 mls, occurred mainly in patients who underwent myomectomy and to a lesser extent total abdominal hysterectomy.

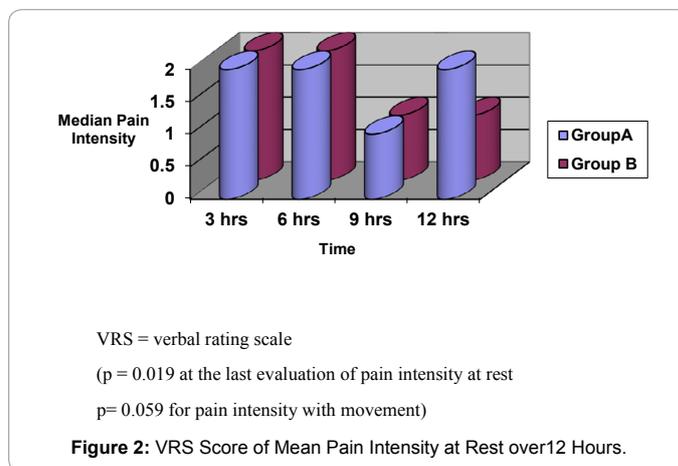
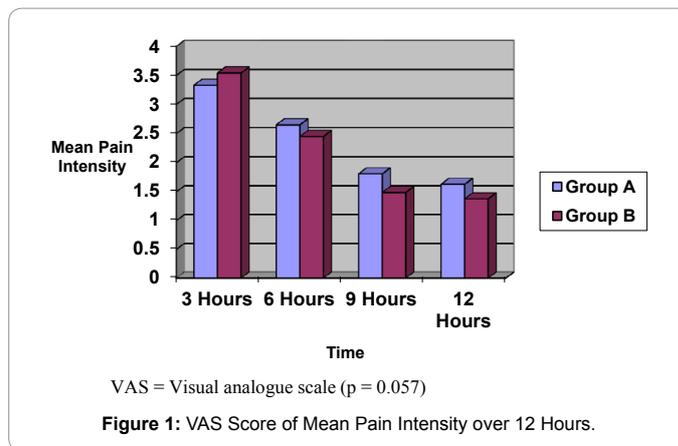
Regarding intra-operative morphine administration, fifty percent (40) of the population received less than 10 mg of Morphine, half of whom belonged to Group B. One member of each group received 20 mg of Morphine. The mean values for Groups A (9.5+4) and B (10.1+4) mgs respectively did not achieve statistical significance ($p=0.8$). There was no significant difference in Morphine consumption in the PACU between Group A (10.5+6.0 mg) and Group B (9.4+5 mg) ($p=0.083$). An increased number of Group B subjects (65%), required less than 10 mg of morphine compared to Group A subjects (50%), however statistical significance was not achieved, ($p=0.8$). The ranges in PACU morphine consumption was similar (5-29 mg) in both groups. The length of surgery did not significantly affect the amount of Morphine administered in the PACU; $p=0.985$.

The total post-operative Pethidine consumption for Group B was 3800 mg compared to 5200 mg for Group A, $p=0.008$. The age of the patient and the length of surgery did not influence the amount of Pethidine administered; p -values 0.338 and 0.131 respectively.

The patients were either fully awake or mildly drowsy at the assessment periods, and demonstrated grossly normal cognitive functions. Nausea and vomiting were reported in four patients in group A and two in Group B. Two in group A were treated with Dimenhydrinate (Gravol), but none in group B required treatment. Vital signs were not significantly different between the groups intra- and post-operatively. Blood transfusion was used for cardiovascular stability in four patients whose blood loss was greater than 1500 mls, especially which their preoperative haemoglobin was less than 12 g/dL.

There was a steady decrease in the VAS score for pain intensity at rest over the periods of assessment for both groups, but more so for Group B which had lower mean scores at the last three assessments periods (Figure 1). However, this did not achieve statistical significance $p=0.057$. At the last evaluation period (12 hours), there was a significant decrease in the VRS for pain intensity at rest, for Group B ($p=0.019$), but no significant difference in pain intensity with movement, $p=0.059$ (Figure 2).

Half the patients in both groups, rated their pain management as 'very good' and none felt that their pain was managed poorly. Although



statistical significance was not attained ($p=0.505$), 28% of patients in the Dexamethasone group rated their analgesia management as excellent compared to 18% in the control group.

Adverse effects which such as; allergic reaction (urticaria, pruritis, bronchospasm), anaphylactic shock or respiratory problems, and hyperglycaemia did not occur in any member of the study population.

Overall, the mean time of discharge after surgery was three (3) days, with a range of 1-8 days. Despite not achieving statistically significance ($p=0.057$), the mean for Group B was 2.7 compared to 3.2 for Group A.

Discussion

Albert Schweitzer, a doctor and philosopher, stated in 1953 that, "We all must die, but that I can save (sic a person) from days of torture, that is what I feel as my great and ever new privilege. Pain is a more terrible lord of mankind than death itself." Knowledge about pain, its pathways and deleterious effects, has increased since Schweitzer's declaration, such that it is regarded as unethical for patients to experience post-operative pain. Delegates of member countries of The International Association for the Study of Pain signed a declaration stating that "Access to Pain Management is a Fundamental Human Right" [17]. The Australian and New Zealand College of anaesthetists have declared pain to be the fifth (5th) vital sign and hence, should be assessed along with the other parameters, i.e. blood pressure, pulse rate, respiration and temperature [18]. Adequate management of acute pain (regardless of the underlying cause), have been found to reduce associated morbidities, including the development of chronic pain

syndrome which has negative socioeconomic impact, both individually and nationally [19,20].

This study showed that most Group B patients (65%) required less than 10 mg of Morphine compared to 50% for Group A in the PACU. This not being statistically significant may be due to the small population of the study. Another likely cause is that the peak anti-inflammatory effect (12-24 hours) of dexamethasone was not attained. As expected, Pethidine requirement was significantly less in the later post-operative period. Statistical significance was achieved for the lower cumulative Pethidine requirement for group B in the 12-hour post-operative period, compared to group A patients. Although the mode for Pethidine consumption for both groups was 100 mg, more patients in Group B received no Pethidine, and more patients in Group A required a total of 200 mg. Patients' age, blood loss, type and length of surgery, were not shown to be confounding factors for Pethidine consumption.

A maximum of 40 mg of Dexamethasone was utilized for this study based on several studies in the literature. Aminmansour et al. demonstrated the efficacy of 40 mg of IV Dexamethasone in significantly reducing opioid requirement post lumbar dissection [19]. Karst et al. found that a range of 20-80 mg was efficacious for their patients who underwent the same procedure [20]. Kardash et al. administered 40 mg Dexamethasone IV pre-operatively to patients undergoing total hip arthroscopy. They concluded that a single dose had a prolonged suppressive effect on the inflammatory response and that it decreased dynamic pain up to 24 hours after surgery [21]. Since no adverse side effect was reported with 40 mg Dexamethasone, the investigators thought it prudent to use this lower effective dose.

Similar to Bisgaard and Karst's studies (4,18), and as expected, there was a steady decrease in the VAS score of Group B patients more than the control group, even though statistical significance was not achieved. The VRS at rest became significantly reduced in the Dexamethasone group at the third (9 hour) post-operative assessment time period and was maintained up to the 12 hour assessment time. The same was not achieved with regards to movement as hypothesized. It was expected that even at the last (12 hour) assessment time point, that this would be achieved. This may be because the full effect of dexamethasone was not achieved and/or that the dose was too low for the study population. This is different from other studies which achieved good quality recovery with smaller doses of Dexamethasone [22-24]. Despite this, the patients overall were satisfied with their analgesic management and none felt that their pain was managed poorly. This most likely is due to the combination of Dexamethasone and adequate administration of Pethidine on the ward. This is substantiated by the fact that more (28%) patients in the Dexamethasone group rated their analgesia management as excellent compared to 18% in the control group, even though statistical significance was not attained. A bigger study population, higher dose of Dexamethasone and/or a second dose post-operatively may have yielded statistical significance.

It is not surprising that no adverse effects were seen. This is most likely due to the following: (i) only a single dose was administered; (ii) the drug and dose have been proven to be safe by other authors/researchers; (iii) it has a low carbohydrate potency (hence minimally causes stimulation of glucose formation); (iv) its sodium retaining potency is low and (v) allergic/anaphylactic reaction is rare [25,26].

The main limitations of the study, is the small population and the relatively short period of follow-up. A longer period (36 hours) of follow up may have shown a significant statistical difference between

the groups, as Dexamethasone has a high [30] anti-inflammatory potency, with peak anti-inflammatory effect at 12-24 hours and duration of action of 36-54 hours [25,26].

Although the population of this study appears small, it has concurred with previous studies that the administration of a single dose of Dexamethasone (0.5 mg/Kg, not exceeding 40 mg) pre-operatively, is safe, reduced opioid requirements post-operatively and positively impacted the satisfaction of a cohort of Jamaican patients. Further studies are needed to assess if a higher dose (without the ceiling of 40 mg), double or multiple doses in a 24 hour period, is safe and will be more efficacious in improving the quality of pain management in local and international populations.

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