

Preoperative Intravenous Dexamethasone and Postoperative Analgesia Following Breast Surgery: A Prospective, Randomized Double-Blind Trial at a Tertiary Healthcare Facility in Ghana

Abstract

Introduction: Breast surgery may be associated with significant postoperative pain and if not adequately treated, may lead to the development of chronic post-surgical pain. This necessitates the use of effective management, involving the use of a multimodal analgesia regimen for the management of post breast surgery pain. The analgesic effect of perioperative use of dexamethasone has been explored but findings have been inconsistent. **Aim:** The aim of this study was to determine the postoperative analgesic enhancing effect of a single preoperative dose of dexamethasone on patients undergoing breast surgery at a tertiary hospital in Ghana. **Materials and Methods:** This was a prospective, double-blind, placebo-controlled study involving 94 consecutively recruited patients. Patients were randomized into two groups: dexamethasone ($n = 47$) and placebo ($n = 47$). Patients in the dexamethasone group had 8mg (2 mL of 4 mg/mL) dexamethasone and those in the placebo group had 2 mL of saline administered intravenously just before induction of anaesthesia. All patients received a standard general anaesthesia with endotracheal intubation.

The numerical rating score (NRS), time to first analgesic request and the total opioid consumed in the first 24 h were recorded. **Results:** Patients receiving dexamethasone had lower NRS scores at all measured time points but this was significant only at 8 h post-surgery ($P = 0.037$). The time to first rescue analgesia was significantly prolonged in the dexamethasone group (339.26 ± 312.90 min vs. 182.10 ± 166.72 min; $P = 0.020$).

However, the mean total opioid (pethidine) consumed in the first 24 h postoperatively was not significantly different between the dexamethasone and control groups (113.75 ± 51.35 mg vs. 100.00 ± 60.93 mg; $P = 0.358$). **Conclusion:** A single preoperative dose of 8mg dexamethasone given intravenously, reduces postoperative pain compared to placebo, significantly reduces the time to first analgesia but not the total opioid consumed in the first 24 h post breast surgery.

Keywords: Dexamethasone, single-dose, preoperative, breast surgery, analgesia, postoperative pain

Trial registration number: PACTR201707002398224

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Introduction

It is estimated that about 40% of breast cancer patients who undergo surgery experience moderate to severe acute pain in the postoperative period.^[1] Acute postoperative pain is managed mainly by the use of parenteral opioids.^[2] In developing countries such as Ghana access to and use of opioids has been found to be low.^[3] Therefore, management of acute postoperative pain after surgery may thus be sub-optimal.

Inadequately treated acute pain results in peripheral and central neuronal sensitization that may evolve into chronic

pain syndromes.^[4] Persistent pain following mastectomy has an incidence of up to 50% and the severity of the acute postoperative pain has been found to be one of the major predictive factors.^[5-7]

A multimodal analgesia regimen will thus be beneficial in reducing opioid requirements, opioid induced adverse effects, provide better postoperative analgesia and reduce the incidence of persistent postoperative pain. Dexamethasone has been suggested as an effective component of a multimodal analgesia regimen after surgical procedures.^[8] The analgesic effect of the perioperative use of dexamethasone has been explored but findings have been inconsistent.^[9]

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Some studies involving a variety of surgeries have demonstrated that a single perioperative dose of dexamethasone results in significant reductions in postoperative pain, postoperative opioid consumption, need for rescue analgesia, and a longer time to first analgesic dose.^[8,10,11] Others have found no analgesic benefits of the use of perioperative dexamethasone.^[12,13] Our study therefore aimed to determine the analgesic effect of a single preoperative dose of dexamethasone on patients undergoing breast surgery.

Materials and Methods

This prospective randomized double-blind trial was conducted between July 2016 and December 2017. The study site is the premiere and largest tertiary care facility in Ghana. It has a total bed capacity of 1800 of which 120 are on the surgical wards. Elective surgical breast procedures done in the hospital include mastectomy with axillary lymph node dissection (ALND), wide local excision with/without (ALND), excision biopsies and microdochectomies.

Ethical considerations

Approval for the study was obtained from the Institutional Review Board, number: KBTH-IRB/00013/2016 and Trial registration number: PACTR201707002398224.

All patients who satisfied the inclusion criteria and provided informed consent were consecutively recruited into the study

Unique and confidential identifiers were assigned to all study participants. Electronic data had password protection and data forms were kept securely. Keys and passwords required to access data were kept by the investigator who also had the codes for the study.

Study population

The inclusion criteria for the study were, patients between the ages of 18 and 70 (inclusive) with American Society of Anesthesiologists (ASA) classes I and II scheduled for breast surgery under general anaesthesia at the Surgical Department of the hospital during the study period.

The following were excluded from the study: patients with known allergy to dexamethasone, history of gestational diabetes or diabetes mellitus, chronic steroid therapy, Immunosuppressed patients and patients on immunosuppressant drugs and patients with advanced breast disease for palliative procedures (e.g. toilet mastectomy). Patients who fulfilled the inclusion criteria but did not meet the exclusion criteria were consecutively recruited into the study. A total of 100 patients were enrolled into the study.

Randomization and blinding

Study participants were randomized into two groups: (A) dexamethasone and (B) placebo by balloting without replacement.

Investigators involved in the data collection and analysis, as well as, the patients were blinded to the interventions.

The code to the study groups was known only to one of the investigators (not involved in data collection and analysis) who only revealed the code after data collection and analysis.

Sample size justification

Previous study has indicated that approximately 20%–68% of patients experience post mastectomy pain syndrome.^[14] Steinhorsdottir *et al.*^[15] indicated incidence of pain (34%) in patients receiving dexamethasone after mastectomy. Assuming 68% incidence of pain in the patients after mastectomy without dexamethasone and 50% reduction in pain for patients receiving dexamethasone after mastectomy, using 90% power at the confidence level of 95%, the sample size of 94 was determined adequate using the formula by Whitley and Ball.^[16]

Description of procedure

At the study site, all patients scheduled for surgery and requiring anaesthesia are reviewed at the pre-anaesthetic clinic where their fitness for anaesthesia is assessed and existing comorbid conditions optimised prior to surgery and anaesthesia. Patients for the study were recruited at the pre-anaesthesia clinic. The principal investigator receives a pre-filled 2-mL syringe labelled “A” or “B” depending on the group a patient had been randomized to from a co-investigator who holds the codes to the identity of the groups. This co-investigator who is not involved in the data collection fills 2-mL syringes with either 2 mL of normal saline or 2 mL of 4 mg/mL (8 mg) dexamethasone both colourless solutions. A dose of 8mg was used as this was found to be effective in a similar study by Gómez-Hernández *et al.* All patients in the study received a general anaesthetic with endotracheal intubation and mechanical ventilation. A blinded Anaesthetist administered the intervention (either 2 mL of normal saline or 8mg dexamethasone) just before induction. Intravenous (IV) midazolam 1 – 2mg, IV fentanyl 1–2 µg/kg and IV propofol 2–3 mg/kg were used for induction of anaesthesia and IV vecuronium 0.1mg/kg used for muscle relaxation. Isoflurane in oxygen/air mixture was used to maintain anaesthesia and intra-operative analgesia was IV morphine up to 0.1mg/kg and IV paracetamol 1g stat.

During the 24-h study period, all patients received IV paracetamol 1 g, 6 hourly and IM pethidine (1 mg/kg) prn for postoperative analgesia as per the postoperative analgesic protocol at the study site. Immediate postoperative (<1 h) pain intensity was assessed at the recovery ward when patient becomes fully conscious and at 4, 8 and 24 h after the surgery using the numerical rating scale (NRS).^[4]

Data handling

Patient demographics, diagnosis and surgical procedure performed, NRS Score, time to first analgesic request and total opioid consumed were recorded on a data extraction form.

Data entry and analysis

To ensure accurate and credible data, source document verification was done. Data of participants who after being recruited into the study showed study protocol violations were censored for removal from data analysis. Data collected was entered into a Microsoft Access database then exported into and analysed using SPSS version 20. Categorical data was summarized as frequencies and proportions and continuous data as means \pm standard deviation. Mean scores of NRS at various times were compared between treatment and control groups using repeated measures analysis of variance (RM-ANOVA). Probability levels < 0.05 were considered significant.

Results

A total 100 patients were enrolled into the study and were randomised Fifty (50) each into the intervention and control groups.

There was complete data for 94 patients, 47 in each arm of the study (case to control ratio of 1:1) which was used in the data analysis as shown in the CONSORT diagram [Figure 1].

The mean (\pm SD) age of the patients was 47.56 ± 11.68 years and majority (96.8%) were females.

There was no significant difference in the demographic characteristics (age, weight, height and BMI), duration of surgery and duration of anaesthesia between the two groups [Table 1].

The amount of opioid (morphine) required intra-operatively between the two groups were not statistically significant (4.68 ± 1.56 vs. 4.79 ± 1.23 , $P = 0.715$). The total opioid (pethidine) consumed within 24h postoperatively did not significantly vary ($P = 0.358$) between the two groups. However, the mean time to first request for rescue analgesia was significantly longer in patients in the dexamethasone group compared to the control group ($P = 0.021$) as shown in Table 3.

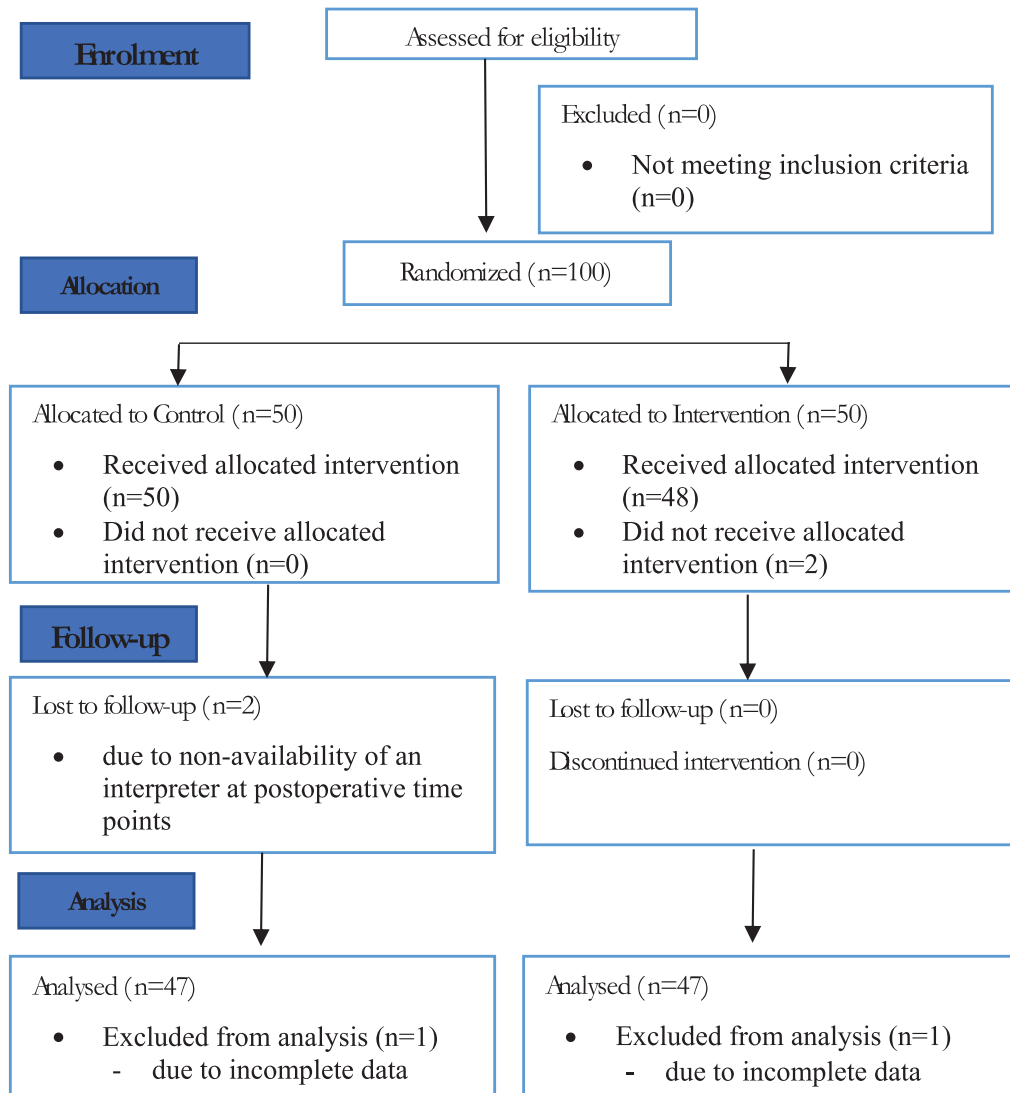


Figure 1: Consolidated standards of reporting trials (CONSORT) diagram

Table 1: Demographic and intra- and postoperative variables of participants between the two groups

Variable	Groups		T-Statistic (df)	P Value
	Dexamethasone Mean ± SD	Control Mean ± SD		
Age (years)	49.55 ± 11.22	45.57 ± 11.91	1.67 (92)	0.099
Weight (kg)	78.43 ± 15.85	78.62 ± 17.67	-0.06(92)	0.956
Height (m)	1.62 ± 0.07	1.60 ± 0.06	1.57(92)	0.119
BMI (kg/m ²)	29.81 ± 5.40	30.53 ± 6.62	-0.58(92)	0.566
Duration of anaesthesia (min)	118.55 ± 38.91	122.94 ± 41.40	-0.53(92)	0.598
Duration of surgery (min)	87.55 ± 37.34	92.23 ± 34.43	-0.63(92)	0.529

BMI = body mass index

The two study groups did not differ in terms of the diagnosis and surgery performed as shown in Table 2

Table 2: Diagnosis and type of surgery between groups

Variable	Groups		Chi-square/Fisher's test	P Value
	Dexamethasone	Control		
Diagnosis	Breast ca	41(87.2%)	2.05	0.662
	Gynaecomastia	0(0.0%)		
	Duct ectasia	2(4.3%)		
	Others	4(8.5%)		
Surgery	WLE + axillary clearance	18(38.3%)	6.24	0.136
	Mastectomy + axillary clearance	20(42.6%)		
	Excision biopsy	3(6.4%)		
	Microdochectomy	1(2.1%)		
	Others	5(10.6%)		
		2(4.3%)		

WLE = wide local excision

There was a progressive decline in mean NRS during the study period in both groups. This decline was significant in both groups ($P = 0.0067$ and 0.0166 respectively). The overall mean NRS score was significantly lower in the dexamethasone group compared to the control group (2.03 ± 1.22 vs. 2.68 ± 1.46 , $P = 0.020$). The mean NRS at all times were lower in the dexamethasone group compared to control group. Differences in the mean NRS recorded between the groups was however only significant at 8 h postoperatively as shown in Figure 2

Table 3: Time to first analgesic request and total postoperative opioid requirement in the two groups

Variable	Groups		T-Statistic (df)	P Value
	Dexamethasone Mean ± SD	Control Mean ± SD		
Postoperative opioid (pethidine [mg])	113.75 ± 51.35	100.00 ± 60.93	0.926(56)	0.358
Time to first request for rescue analgesia (min)	339.26 ± 312.90	182.10 ± 166.72	2.369(92)	0.021

Discussion

The analgesic effect of dexamethasone is thought to be due to its anti-inflammatory properties through a reduction in prostaglandin synthesis.^[17] After major trauma from surgery, there is an inflammatory reaction in which activated macrophages, monocytes, lymphocytes and dendritic cells release a number of cytokines including IL-1, IL-2, IL-4, IL-6, IL-10, IL-12 and TNF- α .^[18] Dexamethasone through its antagonistic action on IL-1, IL-4, IL-6 and TNF- α receptors results in a reduction in the production of these inflammatory cytokines leading to a reduction in oedema and local swelling and therefore pain.^[19]

The pain experienced after breast surgery is of moderate to severe intensity in the acute postoperative period. Fecho *et al.*^[20] found the mean post-anaesthetic care unit (PACU) pain score assessed by using the NRS to be 4.71 ± 0.24 . They also reported approximately 60% incidence of severe acute

postoperative pain (defined as NRS ≥ 5) and this increased with increasing surgical complexity.

In contrast, the mean NRS score in the recovery room/PACU in our study was much lower, being 2.45 ± 1.87 and 3.13 ± 2.79 in the dexamethasone and control groups respectively. In addition approximately 45% of patients had severe pain (NRS ≥ 5) compared with 60% in the study by Fecho *et al.*^[20] The difference was found to be statistically significant ($P = 0.003$) upon hypothesis testing.

Racial differences in the populations studied and cultural factors may account for the observed differences. We studied a homogeneous Ghanaian population as opposed to the mainly Caucasian population enrolled in the study by Fecho *et al.*^[20] In a Singaporean study of women from the three main ethnic groups (Malay, Chinese and Indian), ethnicity and having the mu-opioid receptor (OPRM 1) genotype 118A>G were found to independently predict and

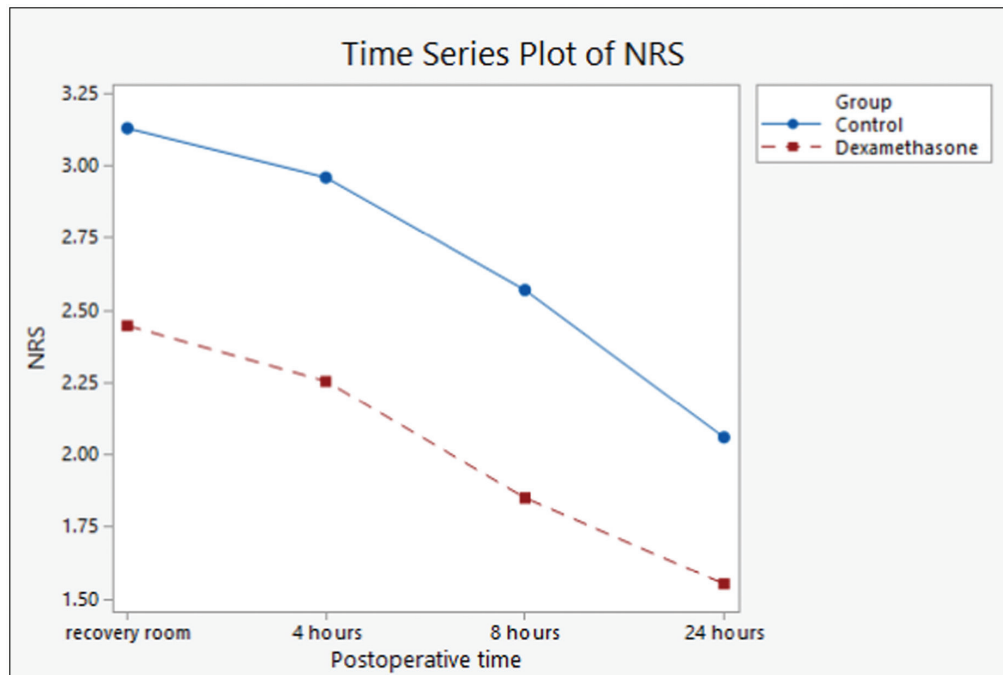


Figure 2: Time series plot of NRS in the first 24h for both groups

contribute to pain perception and postoperative morphine consumption after caesarean delivery.^[21] In a genomic study of Han Chinese women undergoing gynaecological laparoscopic procedures, there was a significant correlation between presence of the single nucleotide polymorphism (SNP) rs6746030 of the SCN9A gene product and higher maximum NRS scores ($P < 0.05$). In addition, there was a significant association between the presence of the tag SNP rs4286289 and both increased postoperative maximum NRS scores ($P < 0.05$) and increased incidence of severe postoperative pain ($P < 0.05$).^[22] These studies lend credence to a racial basis for the variations seen in pain perception and intensity of pain.

Though statistically significant reduction in pain scores between the study groups was only demonstrated at 8h post-surgery, our study revealed the mean NRS scores of patients receiving dexamethasone to be lower at all times postoperatively compared to the control group. In contrast Gomez-Hernandez *et al.*^[23] and Cardoso *et al.*^[24] reported significant reduction in postoperative pain scores at multiple time points. This may be due to a small sample size involved in our study.

The mean time to first opioid analgesic (pethidine) was prolonged in the dexamethasone group compared to the control. This finding is consistent with a meta-analysis by Waldron *et al.*^[9] in which patients treated with dexamethasone had a significantly longer time to first dose of rescue analgesic [mean difference 12.06 min (95% CI: 0.80, 23.32, $P = 0.04$)].

The mean total pethidine (opioid) consumed in the first 24h in the dexamethasone group was 113.75 ± 51.35 mg (11 mg

morphine equivalents) compared to 100.00 ± 60.93 mg (10 mg morphine equivalents). This difference was not statistically significant and contrasts with results of Gomez-Hernandez *et al.*^[23] where the mean dose of intravenous tramadol in patients in the dexamethasone group in the first 24h after surgery, was significantly lower than the controls (36.01 ± 12.62 vs. 55.74 ± 27.36 , $P = 0.03$). This finding of no statistically significant difference in total opioid consumption after preoperative dexamethasone administration in our study contrasts the findings of meta-analysis by De Oliveira *et al.*^[8] and Waldron *et al.*^[25]

Intravenous dexamethasone at doses more than 0.1 mg/kg have been suggested as an effective adjunct in multimodal strategies to reduce postoperative pain and opioid consumption after surgery.^[8] The mean weight of patients in our study was 78.5 kg with a range of 42–126 kg.

Perhaps our fixed dose of dexamethasone used (8 mg) may have been inadequate for some of our patients and could explain our findings. In this study, the intensity of postoperative pain was generally low (mean NRS scores approximately ≤ 3) even among the controls throughout the study period and hence the administration of dexamethasone could not cause any further statistically significant reduction in pain scores among the intervention group. Postoperative opioid consumption has been found to differ among the races and this could also have accounted for the differences observed in our study.^[8,9,23] Our study may also not be powered enough to detect differences in opioid consumption. A larger, more powered study employing the use of dexamethasone at a dose of more than 0.1 mg/kg may thus be need to investigate

the postoperative opioid sparing effects of dexamethasone among patients in Sub-Saharan Africa.

Conclusion

A single preoperative dose of 8mg dexamethasone given intravenously, reduces postoperative pain compared to placebo, significantly reduces the time to first analgesia but not the total opioid consumed in the first 24h post breast surgery.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Authors' contributions

All the authors contributed to the writing of the manuscript. The manuscript has been read and approved by the authors, and all the authors have met the requirements of authorship.

Compliance with ethics guidelines

Approval for the study was obtained from the Institutional Review Board (KBTHIRB), number: KBTH-IRB/00013/2016 and Trial registration number: PACTR201707002398224. The authors also confirm that this study was conducted in compliance with the Helsinki Declaration of 1964 and its later amendments.

All patients who satisfied the inclusion criteria and provided informed consent were consecutively recruited into the study.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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