COMPARISON OF THE TOTAL POST-OPERATIVE RESCUE ANALGESIA BETWEEN ANALGESICS ALONE REGIMEN AND ANALGESICS-ADJUVANT ASCORBIC ACID REGIMEN IN ABAKALIKI, SOUTH-EAST NIGERIA

ABSTRACT

Background: Management of pain postoperatively is a dilemma to the surgeons and anaesthetists. Intravenous ascorbic acid with its antinociceptive and neuromodulatory properties has been found to be an effective adjuvant to multimodal analgesia regimen in reducing the demand for rescue analgesia.

Objective: To compare the total post-operative rescue analgesia between analgesics alone regimen and analgesics-adjuvant ascorbic acid regimen in Alex Ekwueme Federal University Teaching Hospital, Abakaliki.

Study Design: A randomized double blind controlled study involving parturient who received intravenous ascorbic acid as an adjuvant to suppository diclofenac and intravenous paracetamol for post-operative pain management after caesarean section and those who received intravenous sterile water (placebo), suppository diclofenac and intravenous paracetamol for post-operative pain management after caesarean section.

Methodology: A total of 164 parturient who satisfied the inclusion criteria were recruited for the study by systematic sampling. These were equal number of 82 participants in each group. Group A received intravenous ascorbic acid as an adjuvant to suppository diclofenac and intravenous paracetamol for post-operative pain management while Group B received intravenous sterile water (placebo), suppository diclofenac and intravenous paracetamol. The results were analyzed using SPSS version 26 with appropriate tables and figures generated.

Results: The mean pain score at 2 hours after surgery was significantly higher in Group B when compared with Group A (6.9 ±1.4 vs.3.2 ±1.5; P<0.0001). At first request for analgesia, the mean NRS was significantly higher in Group B compared to Group A (6.9 ±0.9 vs.6.1 ±0.7; P<0.0001). Time to first request for analgesia was longer for parturient in Group A (180.6 ± 65.6 mins) than those in group B (92.4± 35.4 mins; P<0.0001). Group B participants 48 (58.5%) requested for rescue analgesia twice against 25 (30.5%) in Group A(P=0.007).

Conclusion: Demand for post-operative rescue analgesia due to moderate and severe pain was higher in participants who received analgesics alone regimen as opposed to their analgesics-adjuvant ascorbic acid regimen counterparts.

Recommendation: Multi-center clinical trials are needed to strengthen the evidence provided by this study.

KEYWORDS: Ascorbic acid, Adjuvant, Post-Operative, Regimen, Analgesics, Analgesia, Rescue analgesia, Intravenous.

INTRODUCTION

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[1] Pain and its threshold are subjective and vary among individuals. According to World Health Organisation, pain management is an inalienable human right.[2] Optimum post-operative pain management has remained a daunting challenge facing both surgeons and patients as complaints of unrelieved pain remains a source of concern following surgery. Post-operative pain is usually described as severe especially within the first twenty-four hours after surgery, it can be distressing with possible psychological trauma on the individual.

Inadequately managed post-operative pain may result in negative sequelae such as emotional anguish, depression, insomnia, impaired maternal bonding and lactation, urinary retention, poor wound healing, reduced quality of life, prolonged hospitalization, increased cost of care, patient dissatisfaction with quality of healthcare, post-traumatic stress disorder and development of chronic pain syndrome.[3] The incidence of acute post-operative pain remains high though under-reported especially in resource poor settings.[4] The United States Institute of Medicine reported that as much as 80% of surgical patients experience post-operative pain, with 88% of these described as moderate to severe pain.[4] Similar study showed an incidence of 86% with 75% of it reported as moderate to extreme in the immediate post-operative period.[5] A survey in Rwanda on post-operative pain management showed a pain score of greater than 6 (severe pain) in 46% of the patients while a similar Nigerian study showed that a high proportion of surgical patients experience moderate to severe pain and more among female patients (58%).[6,7]

The resumption of the concept of multimodal analgesia has revolutionized the approach to pain management.[8,9] This has helped reduce opioids overdependence in perioperative pain management and its attendant side effects.[8,9] Non-steroidal anti-inflammatory drugs (NSAID) such as rectal diclofenac and intravenous paracetamol have been employed in postoperative pain management with positive outcomes.[8] In addition, adjuvants such as ascorbate that exert neuromodulatory and antinociceptive effects on the central nervous system has been used to potentiate the analgesic effects of these drugs. [9]

The use of Vitamin C as an adjuvant has shown positive results in pain management for various kinds of pain, such as post-operative pain, post-herpetic pain and chronic pain syndrome.[10] Being an anti-oxidant and neuroprotective agent, its incorporation into the multimodal approach to the management of various kinds of pain has yielded encouraging results and this has served to minimize the side effects of a single drug, reduce dosing and maximize the benefit of synergistic effects of other agents by their different mechanisms of actions.[10,11]

Studies on this topic particularly in Sub-Saharan Africa are scarce and caesarean section rate in Nigeria is increasing; about 16.4 - 35.9%. [12,13] The aim of this study is to compare the total post-operative rescue analgesia between analgesics alone regimen and analgesics-adjuvant ascorbic acid regimen in Alex Ekwueme Federal University Teaching Hospital, Abakaliki. This will also add to the body of knowledge on the role of intravenous ascorbic acid as a cost-effective adjuvant to post operative analgesia in Sub-Saharan Africa and medical practice in general.

METHODOLOGY

Study Area: The study was conducted at Alex Ekwueme Federal University Teaching Hospital Abakaliki, Ebonyi State, South East Nigeria. It is a Federal Tertiary Health Care Institution with a 720-bed capacity that provides both general and specialist services to the people of Ebonyi state. It is a training and research center and also serves as a referral center for Ebonyi State as well as sub -serving neighboring states such as Cross Rivers, Abia and Enugu States.

Study Population: The study population were parturient aged 18-40 years with American Society of Anesthesiologists physical status I-II who had scheduled elective caesarean delivery under spinal anaesthesia at the study centre.

Inclusion Criteria: Consented parturients aged 18-40 years with American Society of Anesthesiologists physical status I-II scheduled for elective caesarean delivery under spinal anaesthesia at the study centre.

Study Design: The study was a prospective double - blind randomized controlled study involving two arms namely; parturients who received intravenous ascorbic acid (Vitamin C) as an adjuvant to suppository diclofenac and intravenous paracetamol for post-operative pain management after caesarean delivery under spinal anaesthesia (Group A) and those who received intravenous sterile water (placebo), suppository diclofenac and intravenous paracetamol for post-operative pain management after caesarean delivery under spinal anaesthesia (Group B).

Study Tool: The study tool was data collection sheets.

Sample Size: The sample size was 164 comprising 82 eligible parturients who received intravenous ascorbic acid (Vitamin C) as an adjuvant to suppository diclofenac and intravenous paracetamol for post-operative pain management after caesarean delivery under spinal anaesthesia and 82 eligible parturients who received intravenous sterile water (placebo), suppository diclofenac and intravenous paracetamol for post-operative pain management after caesarean delivery under spinal anaesthesia. It was determined by a previously validated formula for randomised control trial.[14]

Sampling Technique: The sampling method was systematic sampling. After obtaining consent from those who meet the inclusion criteria, the first eligible participant who was the starting point of selection was recruited randomly. The interval for the selection of other participants was derived from the sampling fraction which was obtained by dividing the study population by the sample size. The sampling fraction was used to recruit other participants until the sample size was complete.

Patients Recruitment: Having obtained informed consent to participate in the study from eligible participants, Allocation of the participants into the treatment and control arm was done by the two research assistants using a set of blocks A and B, and they were assigned serial numbers till the number of participants required for the sample size was complete. The researcher and the parturients were blinded to the allotment. The two research assistant who were also the allocators hid the blocks from the researcher and randomly mixed block sizes in order to avoid bias.The study solutions were prepared to have the same volume and drawn into identical 10ml syringes by a pharmacist who was not part of the study. Only the research assistants knew the grouping and the research drugs given to the groups. This was never disclosed to the researcher or the

participants. The research assistants were two junior resident doctors who were trained about the study protocol (such as the contents of the information sheet, consent form, data collection sheet and also sample collection) daily for one week before commencement of the study.

Data Collection

Following informed consent from the participants, detailed history of each patient, including medical history, family and social history, the history of any current illness, and the history of previous anaesthetic exposure were obtained and documented in the data collection sheet. Full general and systemic examination was also conducted. These were done to help determine patients who met the inclusion criteria for the study and also access fitness for surgery and anaesthesia. Patients' weight and height was recorded in the data collection sheet. Investigations such as full blood count (FBC) to check for preoperative haemoglobin (or packed cell volume) and platelet count necessary for perioperative haemostasis were done and reviewed for each patient. Other investigations including urinalysis, serum electrolyte, urea and creatinine were also done for each of the patient. Paturient's physical fitness for anaesthesia and surgery was determined using American Society of Anesthesiologist (ASA) classification

Each parturient received 150 mg of oral ranitidine in the evening before surgery. They were educated on fasting guidelines of taking only clear water 2 hours before surgery, light/semi solid food 6 hours before surgery and solid food 8 hours before surgery and were subsequently fasted accordingly. Each parturient was adequately educated on the Numerical Rating Scale (NRS)[10] . The researcher filled data collection sheet with corresponding codes, and ensured the activities of the research assistants involved in the study were well coordinated and administered the drugs to ensure uniformity in the technique. Blinding and randomization were strictly adhered.

On the morning of surgery patients were transported to the theatre on a trolley in the left lateral position. Anaesthetic machine, ancillary equipment and suction machine were checked for functionality and accessibility and alarms limits and volumes set. General anaesthetic agents such as intravenous ketamine, propofol, suxamethonium, Isoflurane were made available in case it becomes necessary to convert to general anaesthesia. Emergency tray containing endotracheal tube of various sizes, adrenaline and other emergency drugs were also made available. Neonatal resuscitation unit was assessed for functionality of oxygen and heat source for regulation of neonate's ambient temperature. Baseline pulse rate, non-invasive blood pressure (NIBP), respiratory rate, oxygen saturation and electrocardiography readingswere taken using the multi-parameter monitor (Mindray MEC-100) and recorded. All the patients received intravenous (IV) metoclopramide 10mg and IV ranitidine 50mg. 1000ml (10ml/kg) of 0.9% saline solution was given over 15-30 minutes prior to spinal anaesthesia as preload. Spinal anaesthesia was performed under strict aseptic technique with patient in sitting position; hip and knee flexed knee level above the hip and elbows placed on ipsilateral thigh. Patient back was scrubbed with 0.5% chlorhexidine and methylated spirit and draped. The L_3/ L_4interspace was located using the iliac crest as landmark and the skin infiltrated with 2ml of 2% lidocaine. A 25G Whitacre spinal needle was inserted via a midline approach with an introducer into the subarachnoid space evidenced by appearance of cerebrospinal fluid (CSF) at the spinal needle shub and 2ml of 0.5% hyperbaric bupivacaine was then gently injected. The spinal needle was removed and haemostatic dressing was placed over the injection site. After injection of the hyperbaric bupivacaine, the patient was gently returned to the supine position with a pillow under the patient's shoulder and a 15^0 wedge under the right hip for left uterine displacement. The level of the sensory neurological block was accessed using cotton wool soaked in spirit and pin prick test with a short bevel needle along the mid axillary line

bilaterally at 2 and 5 minute[40,41]. Bromage score was used to assess the level of motor block of the lower limbs[42]

A systolic blood pressure of <90mmHg or <30% of baseline after spinal injection was considered as hypotension and treated by increasing the rate of intravenous fluid administration and administration of intravenous ephedrine in 3mg aliquots if hypotension is refractory to intravenous fluid administration. Intra-operative monitoring and recording of blood pressure, pulse rate, peripheral oxygen saturation of blood, electrocardiography was done using the multiparameter monitor (Mindray MEC 100) and blood pressure recorded within 2 minutes after the subarachnoid block, then every 5minutes up to the end of the surgery. Blood loss and urine output were monitored and recorded. Intravenous oxytocin 10 IU was administered after delivery of the baby and clamping of the umbilical cord. 10 IU bolus of oxytocin was given intravenously and an additional 40 IU was put in 0.5litre of 0.9% saline solution to be infused at 125ml/hour. After delivery of the foetus, the foetal outcome was assessed using the Apgar scoring system in 1st, 5th and 10th minutes by the paediatrician for each neonate.
At the end of the surgery, group A (n = 82) participants received suppository diclofenac 100mg, intravenous paracetamol 600mg, and stat dose 1g(10ml) intravenous vitamin C. Group B (n = 82) participants received suppository diclofenac 100mg, intravenous paracetamol 600mg, and stat dose 10ml sterile water intravenously. The drugs were administered by the researcher who was blinded to the drugs being administered. Participants were transferred to the recovery room for observation for 45mins by the researcher[43]. They were monitored for pain using the NRS. Vital signs (HR, SBP, DPB and MAP) were monitored every 5 minutes by the researcher for 1 hour before transferring to the ward. Participants' pain scores were monitored using the NRS. In addition to the above, side effects (nausea, vomiting, abdominal cramps and headache) were also monitored over the first 24 hours post operatively in the ward by the researcher with the assistance of senior nursing staff of the ward that were recruited and adequately briefed on the study.
Following transfer to the post-natal ward, pain was assessed at 2, 6, 12, 18 and 24 hours respectively. Assessment at late hours of the night was done by the senior registrars on call duty who were adequately briefed on the study but were blinded to the groups.

The pain severity was recorded using the numerical rating scale: 0 -10, where 0 is no pain 5 moderate pain and 10 is the worst pain imaginable. Rescue analgesia of IV Tramadol 100mg was given whenever pain score exceeded 4 and on request. Post operative analgesics in the ward comprising IV paracetamol (600mg 6hourly), IM pentazocine (30mg 8 hourly) and intramuscular diclofenac (75mg 12 hourly) were also administered as per the post-operative analgesia protocol of the managing team and the time of administration of the drugs documented in the data collection sheet.
Data Analysis: The data were analyzed using IBM SPSS software package, version 26.0 (IBM Corp., Armonk, NY). Categorical variables such as ASA, side effects and patient's satisfaction were presented as numbers (representing frequencies) and percentages and analyzed using Chi square χ^2-test or Fisher's exact where applicable. However, where cells were less than 5 non-parametric (Kruskal Wallis (H) test was used. Continuous variables such as age (years), gestational age (weeks), weight (kg), height (m), haemodynamic parameters, time to first additional analgesic request, and Numerical Rating Scale were reported as mean and standard deviation. Independent Sample's *t*-test was used to compare mean differences between the two study groups for normally distributed continuous variables. Significance of the results was set at the 5% level. Kolmogorov-

Smirnov test and Q-Q plot were used to test for normality. Results were presented using tables and figures.

Ethical Consideration: An institutional approval for this study was obtained from the Ethical Review Committee of Alex Ekwueme Federal University Teaching Hospital Abakaliki. Informed written consent was obtained from each participant after adequate counselling and the data obtained from the study were treated with confidentiality and used solely for the purpose of the study.

Limitation of the study:

1. Dose-response or the effect of continuation of therapy on pain was not evaluated due to the difficulty of patients' follow-ups.
2. Despite the use of a valid pain instrument for pain assessment, subjective assessment of pain may not be 100% reliable.
3. Other factors that could influence pain, such as psychological and cultural factors were not explored.

RESULTS

Participants recruited into the study were 164. They were randomized into two equal groups with eighty-two 82 participants in each group. The study group (A) received 1g (10ml) Intravenous Ascorbic acid after surgery in addition to 100mg rectal diclofenac and 1g intravenous paracetamol and the control group (B) received 10 ml sterile water post-surgery in addition to 100mg rectal diclofenac and 1g intravenous paracetamol.

TABLE I: GENERAL PROFILE OF THE STUDY POPULATION

Table 1 showed the general profile of the study population. The overall mean age of the patients in the study population was 32.6 ± 4.6 years while the mean age in group A vs group B was 32.6 ± 4.6 years vs. 32.7 ± 4.7 years. The difference was not statistically significant (P=0.906). The mean gestational age between both groups was comparable; 39.2 ± 1.1 weeks vs. 39.0 ± 0.9 weeks in group A and group B respectively (P= 0.197). Majority of the patients (39 vs. 49) in both groups were multiparous (A = 39 vs. B = 49, representing 47.6% and 59.8% respectively; P = 0.286). Both groups were comparable in respect of their anthropometric parameters mean weight (71.7±6.7kg vs 71.3±6.7kg; P=0.689), mean height (169.1±4.1 vs, 169.1±3.2; P=0.950) and Body mass index (25.1±2.5kg/M^2 vs. 25.0±2.5 kg/M^2; P=0.678). Similarly, the hemodynamic profiles of both groups were similar: SBP (115 ±11.5 vs. 117.2±7.9mmHg; P=0.382), DBP (69.1±9.4mmHg vs. 69.4±10.0mmHg; P=0.834) and MAP (85.1±7.9mmHg vs. 85.9±8.0mmHg, P=0.505). The mean duration of surgery (61.1±14.4min vs. 64.3±19.4 min; P=0.231) was statistically comparable in the two groups.

TABLE 2: OPERATIVE CHARACTERISTICS IN THE STUDY GROUPS

Operative Characteristics in the study groups was presented on table 2. Most of the participants in this study had a history of previous caesarean section. Although the number of women with previous caesarean sections in the control group B (49/82=57.8%) were higher than those in group A (32/82=39.0%); but the difference in their proportion was not statistically significant (P=0.059).

TABLE 3: POST-OPERATIVE PAIN SCORE IN THE FIRST 24 HOURS USING THE NUMERICAL RATING SCALE (NRS) PAIN SCORE

The assessment of pain between the study population and control group was represented in table 3 and 4. The mean pain score using NRS at 2 hours was significantly higher in group B when compared to group A (6.9 ±1.4 vs.3.2 ±1.5; P<0.0001). Conversely the mean pain score at 6hours was significantly higher in group A when compared to group B(5.8±1.1 vs 5.4 ±1.0; P< 0.003). At 12 hours, mean pain scores was lower in group A compared to B (4.5 ±0.9 vs. 4.7 ±1.1; P=0.145); however, the mean differences in the pain assessments at 18 hours (3.7 ±1.0 vs 3.9 ±0.9; P=0.195) and 24 hours (2.5 ±1.0 vs. 2.5 ±0.9; P>0.999) were statistically comparable. But at the first request of analgesia the mean NRS was significantly higher in group B compared to group A (6.9 ±0.9 vs.6.1 ±0.7; P<0.0001).

TABLE 4: GRADING OF POST-OPERATIVE PAIN SCORE AT DIFFERENT HOURS AND AT THE FIRST REQUEST OF ANALGESIA USING NRS

The result on table 4 showed that at 2 hours; 55 (67.1%) of participants in the group A complained of mild pain, 23 (28.0%) complained of moderate pain while only one participant representing 1.2% complained of severe pain compared to 15 (18.3%) who had moderate pain and 65 (79.3%) that complained of severe pain among patients in group B and this difference was statistically significant (P<0.0001).

At 6 hours post surgery, 70 participants in group B representing over 85% complained of moderate pain as compared to 60 (73.2%) in group A. Furthermore, 17 (20.7%) participants in group A and 11 (13.4%) group B complained of severe pain at 6 hours. No participant in group A complained of severe pains at 12 hoursas compared to 7 (8.5%) in group B. At 18 hours and 24 hours following caesarean section no participant complained of severe pains.

As at the time participants requested for analgesia for the first time (NRS greater than four), almost two-thirds of the patients in group B (>60%) had complained of severe pains as against only 16 (19.5%) in group A. The differences in their proportions were statistically significant.

TABLE 5: TIME TO FIRST ANALGESIC REQUEST IN BOTH GROUPS

Table 5 showed that it took a longer time for patients in group A (180.6 ± 65.6 mins) to request for first (rescue) analgesia following caesarean section than patients in group B (92.4± 35.4 mins). The mean difference of 88.1 (95% CI: 71.9- 104.3) mins was highly significant P<0.0001.

TABLE 6: DEMAND/REQUEST FOR RESCUE ANALGESIA (IV TRAMADOL100mg) IN THE FIRST 24 HOURS

The results documented on table 6 revealed that patients in group A requested for rescue analgesics fewer than those in group B. The results showed that 4 patients (4.9%) did not request for rescue analgesia in group A. In group A, 53 (64.6%) compared to 29 (35.4%) in Group B requested for rescue analgesia only once (P=0.008); on the contrary significantly higher proportion of patients in group B 58.5% requested for rescue analgesia twice against 30.5% in group A, (P=0.007). five patients (6.1%) in group B requested for rescue analgesia thrice while none of the patients in group A requested for rescue analgesia more than twice. Meanwhile, 75 patients (91.5%) in group A and 55 (67.1%) in Group B were given IV 100 mg of tramadol once. The difference was not statistically significant (P=0.079). Only 3 (3.7%) of the patients in group A were administered IV 100mg tramadol twice as compared to 27 (32.9%) in group B had IV 100 mg tramadol twice, the differences were statistically significant (P<0.0001).

TABLE 7: TOTAL RESCUE ANALGESIA REQUIREMENTS IN BOTH GROUPS IN THE FIRST 24 HOURS AFTER CESAREAN DELIVERY

Total dose of rescue analgesia was represented on table 7. Four (4.9%) of the patients in group A did not request for rescue analgesia within the first 24 hours. Over 92% (76/82) of the patients in group A were given intravenous 100 mg of tramadol as compared to almost 66% (54/82) of group B to mild to moderate pain within the same period; the difference was not statistically significant (P=0.054). Only 2 patients (2.4%) in group A as against 28 (34.1%) in group B were administered 2 doses of analgesics as a result of moderated to severe pain. This difference was statistically significant (P<0.0001).

Table 1: General characteristics of patients in the study groups

Indication	**Group A n= 82**	**Group B n= 82**	**Test of statistics**	**P**
Age (years); Mean± SD	32.6±4.6	32.7±4.7	t=0.118	P=0.906*
Parity:				
0 ; N (%)	26 (31.7)	17 (20.7)	X^2=1.884	P=0.170*
1 ; N (%)	16 (19.5)	16 (19.5)	X^2=0.001	P>0.999*
2-4 ; N (%)	39 (47.6)	49 (59.8)	X^2=1.136	P=0.286*
≥5 ; N (%)	1 (1.2)	0 (0.0)	-	-
Gestational age (weeks)	39.2 ± 1.1	39.0 ± 0.9	t=1.296	P=0.197*
Weight (Kg); Mean± SD	71.7±6.7	71.3±6.7	t=0.401	P=0.689*
Height (cm); Mean± SD	169.1±4.1	169.1±3.2	t=0.063;	P=0.950*
BMI (Kg/M^2); Mean± SD	25.1±2.5	25.0±2.5	t=0.416	P=0.678*
SBP (mmHg); Mean± SD	115 ±11.5	117.2±7.9	t=0.933	P=0.382*
DBP (mmHg); Mean± SD	69.1±9.4	69.4±10.0	t=0.210;	P=0.834*
Duration of surgery (min) ; Mean± SD	61.1±14.4	64.3±19.4	t=1.202	P=0.231*
Estimated Blood loss (ml) ; Mean± SD	418.1±60.8	397.7±66.1	t=2.053	P=0.042**

**- Differences in mean/frequencies not statistically significant at P>0.05*

***- Differences in mean/frequencies not statistically significant at P<0.05*

t- Student's Independent t test, X^2*- Chi square test value and P: level of significance*

Table 2: Operative Characteristics in the study groups

INDICATION FOR SURGERY	Group A Frequency	(%)	Group B Frequency	(%)
Anencephaly with unfavorable cervix	1	1.2	0	0
Bad Obstetric History(BOH)	1	1.2	4	4.9
Borderline Pelvis	3	3.7	1	1.2
Breech+ Macrosomia	1	1.2	0	0
Breech at term	8	9.8	4	4.9
Cephalopelvic disproportion	1	1.2	4	4.9
Elderly primigravida	2	2.4	1	1.2
Gestational Diabetes Mellitus	2	2.4	0	0
Borderline pelvis + macrosomia	1	1.2	0	0
Cephalopelvic disproportion+ macrosomia	0	0	2	2.4
Macrosomia	5	6.1	2	2.4
Macrosomia + post date	2	2.4	0	0
Malpresentation	2	2.4	0	0
Maternal request	6	7.3	2	2.4
Persistent occipito posterior position	0	0	2	2.4
?Pregnancy Induced Hypertension(PIH)	0	0	1	1.2
Type 1 Placenta previa	4	4.9	2	2.4
Previous myomectomy	0	0	1	1.2
Post date	4	4.9	1	1.2
Precious baby	0	0	1	1.2
Post date + unstable lie	1	1.2	0	0
Previous CS	23	28	40	48.8
Previous CS + Breech	0	0	2	2.4
Previous CS + advanced age	1	1.2	1	1.2
Previous CS + Bad Obstetric History(BOH)	1	1.2	0	0
Previous CS + unstable lie	2	2.4	0	0
Previous CS + previous myomectomy	1	1.2	1	1.2
Previous CS + Retro Viral Disease(RVD) on Highly Active Anti Retroviral Therapy	0	0	1	1.2
Previous CS+ post date	3	3.7	0	0
Previous scar	0	0	3	3.7
Previous CS+ macrosomia	1	1.2	2	2.4
Transverse lie	5	6.1	1	1.2
Transverse lie + previous CS	0	0	2	2.4
Unstable lie at term	1	1.2	0	0

Type 2 Placenta Previa	0	0	1	1.2

Table 3: Post-Operative Pain Score at different Hours and at the first request of analgesia using NRS

Pain score (Mean ±SD [range])	GROUP A N=82	GROUP B N=82	T	P
NRS at Baseline	0 [0-0]	0 [0-0]	-	-
NRS at 2hours	3.2 ±1.5 [0-7]	6.9 ±1.4 [0-9]	16.571	<0.0001**
NRS at 6hours	5.8±1.1 [3-8]	5.4 ±1.0 [3-8]	2.991	0.003**
NRS at 12hours	4.5 ±0.9 [2-6]	4.7 ±1.1 [3-7]	1.465	0.145*
NRS at 18hours	3.7 ±1.0 [2-6]	3.9 ±0.9 [2-6]	1.300	0.195*
NRS at 24hours	2.5 ±1.0 [1-5]	2.5 ±0.9 [1-4]	0.001	0.999*
NRS at the first request of analgesia	6.1±0.7 [5-8]	6.9±0.9 [5-9]	6.488	<0.0001**

**- Differences in mean/frequencies not statistically significant at P>0.05*
***- Differences in mean/frequencies not statistically significant at P<0.05*
t- Student's Independent t test

Table 4: Grading of Post-Operative Pain Score at different Hours and at the first request of analgesia using NRS

Pain score	GROUP A N=82	GROUP B N=82	Test of statistic	P
NRS at Baseline			-	-
No pain; N (%)	82 (100/0)	82 (100.0)		

NRS at 2h				
No pain; N (%)	3 (3.7)	2 (2.4)		
Mild pain; N (%)	55 (67.1)	0 (0.0)		
Moderate pain; N (%)	23 (28.0)	15 (18.3)		
Severe pain; N (%)	1 (1.2)	65 (79.3)	H=108.646	<0.0001**
NRS at 6h	5 (6.1)	1 (1.2)		
Mild pain; N (%)	60 (73.2)	70 (85.4)		
Moderate pain; N (%)	17 (20.7)	11 (13.4)	H=0.222	0.637*
Severe pain; N (%)				
NRS at 12h				
Mild pain; N (%)	12 (14.6)	12 (14.6)		
Moderate pain; N (%)	70 (85.4)	63 (76.8)		
Severe pain; N (%)	0 (0.0)	7 (8.5)	H=1.201	0.237*
NRS at 18h				
Mild pain; N (%)	32 (39.0)	29 (35.4)		
Moderate pain; N (%)	50 (61.0)	53 (64.6)	X^2=0.235	0.628*
NRS at 24h				
Mild pain; N (%)	70 (85.4)	67 (81.7)		
Moderate pain; N (%)	12 (14.6)	15 (18.3)	X^2=0.399	0.528*
NRS at the first request of analgesia				
Moderate pain; N (%)	66 (80.5)	31 (37.8)		
Severe pain; N (%)	16 (19.5)	51 (62.2)	X^2=30.912	<0.0001**

**- Differences in mean/frequencies not statistically significant at P>0.05*

***- Differences in mean/frequencies not statistically significant at P<0.05; H-Kruskal Wallis;* X^2*- Chi square test value and P: level of significance*

Table 5: Time to first analgesia request

	Group A Mean ± SD	Group B Mean ± SD	Test of statistic	P
Time first analgesia was requested for/given (min)	180.6±65.6	92.4± 35.4	t=10.703	P<0.0001**

***- Differences in mean/frequencies not statistically significant at P<0.05*

t- Student's Independent t test; P: level of significance

Table 6: Number of times rescue analgesia was requested and given

Indication	Group A	Group B	Test of statistic	P

Number of times rescue analgesia was requested for				
0; N (%)	4 (4.9)	0 (0.0)	-	-
1; N (%)	53 (64.6)	29 (35.4)	X^2=7.024	0.008**
2; N (%)	25 (30.5)	48 (58.5)	X^2=7.247	0.007**
3; N (%)	0 (0.0)	5 (6.1)	^	^
Number of times rescue analgesia was actually given				
0; N (%)	4 (4.9)	0 (0.0)	^	^
1; N (%)	75 (91.5)	55 (67.1)	X^2=3.077	0.079*
2; N (%)	3 (3.7)	27 (32.9)	X^2=19.200	<0.0001**

- *Differences in mean/frequencies not statistically significant at P>0.05
****- *Differences in mean/frequencies not statistically significant at P<0.05***
X^2*- Chi square test value and P: level of significance*

^*- statistic not computed because values in both groups were equal or one the cells was zero*

Table 7: Total dose of rescue analgesia (IV 100 mg Tramadol) given within 24 hours

Analgesia (IV 100 mg Tramadol) Given	Group A n=82	Group B n = 82	Test of statistic	P
0; N (%)	4 (4.9)	0 (0.0)	^	^
1; N (%)	76 (92.7)	54 (65.9)	X^2= 3.723	P=0.054*
2; N (%)	2 (2.4)	28 (34.1)	X^2= 22.533	P<0.0001**

- *Differences in mean/frequencies not statistically significant at P>0.05
****- *Differences in mean/frequencies not statistically significant at P<0.05***
X^2*- Chi square test value and P: level of significance*

^*- statistic not computed because values in both groups were equal or one the cells was zero*

DISCUSSION

This study showed that intravenous Vitamin C was effective in reducing pain perception and intensity. Vitamin C also demonstrated the ability to prolong the time for administration of first rescue analgesic while minimizing the demand for rescue analgesics in the first 24 hours after surgery in parturients who had elective caesarean delivery under spinal anaesthesia. This is in agreement with other studies on the effectiveness of Vitamin C as an antinociceptive agent[15-17].

Parturients who received intravenous Vitamin C in this study showed pain scores that where significantly lower especially within the first two hours after surgery compared to the placebo group. Their cumulative pain score at twenty four hours was also less though not statistically

significant. This was similar to findings of the meta-analysis study by Hung et al; a pooled analysis of their study showed a significant reduction in pain score in the participants who received intravenous Vitamin C compared to those who received a placebo[18]. This observed lower pain score was more at two hours post operative with overall reduction in twenty-four hours postoperative pain score[18]. Similarly Kumar et al in their study on the effect of Vitamin C on laparoscopic surgeries, showed that in the immediate post operative period, patients who received Vitamin C had a lower visual analogue pain score of 2.14±0.51 compared to the placebo group with visual analogue score of 2.88±1.07 and concluded that Vitamin C reduced pain in the immediate postoperative period[19]. Furthermore, Jeon et al in a study on the effect of Vitamin C on laparoscopic surgery found that participants who received intravenous Vitamin C when compared to placebo group showed decreased postoperative pain at rest during the first two hours and up to twenty-four hours after surgery[20]. A research by moon et al on the evaluation of the analgesic effect of Vitamin C on post laparoscopic shoulder tip pain found out that patients who received Vitamin C had lower lower incidence of post laparoscopic shoulder tip pain compared to the placebo group within the first twenty-four hours[21]. Similarly, Schencking et al in a multi-centre study on the effect of intravenous Vitamin C in the treatment of shingles concluded that addition of Vitamin C to the treatment regimen was associated with a decline in the observed visual analogue scale within two to twelve weeks of treatment[22]. The observed decrease in pain score in these studies may be attributable to the neuromodulatory and antinociceptive effects of Vitamin C. This mechanism is thought to be via inhibitory modulation at N methyl D-aspartate (NMDA) receptors that regulate glutamate. This finding is thus consistent with the available evidence that Vitamin C is effective in ameliorating pain[23-25].

The first time to request rescue analgesic in this study was found to be significantly prolonged in those that received intravenous Vitamin C than in those that were given a placebo. This is in accordance with results obtained by Kumar et al who concluded that a significantly higher proportion of patients who received placebo requested for rescue analgesia within the first hour after surgery when compared to those in the study group[19]. This significant disproportion may be attributed to the effect of Vitamin C in down regulating nociception in the brain[25,26] . A study by Aweke et al found that the time to first request for rescue analgesia was prolonged in the tramadol based study group than the NSAID only group[27]. Their observed duration to first request for analgesia was comparatively of a shorter time frame than that of the Vitamin C group in the index study. This buttresses the fact that the addition of Vitamin C as an adjuvant potentiates the effect of other analgesics, thus prolonging the time to request for rescue analgesia[28,29].

The number of times rescue analgesia was requested for was lower in Vitamin C group than in placebo group. This study outcome showed that a significantly higher proportion of placebo group parturients required more rescue analgesia than their Vitamin C counterpart. Manuel et al conducted a meta analytic review on the efficacy and safety of Vitamin C in non cardiac surgery and found that administration of Vitamin C was associated with a significantly less demand for supplemental rescue analgesia[30]. This outcome is similar to the study by Kumar et al on two hundred patients presenting for various kinds of laparoscopic surgeries[19]. They studied the effect of Vitamin C as a premedicant in reducing analgesia requirements following laparoscopic surgeries and their finding showed that whereas only six patients out of one hundred participants required rescue analgesia in the study group, forty-one patients of the one hundred in the control group required rescue analgesia within 30 minutes after surgery. Furthermore, Jeon et al in their study also agreed to the fact that intravenous Vitamin C was effective in reducing postoperative

pain as observed with a reduction in the amount of demand for rescue analgesia in the study group compared to the control group[20]. Also Moon et al concorded with the observation that the administration of Vitamin C was responsible for a reduced demand for rescue fentanyl in their study group compared to the control group[21]. Conversely, a study by mitra et al that involved diclofenac plus tramadol, and diclofenac plus paracetamol showed no statistically significant difference in demand for rescue analgesic requirement in the two groups[31]. These finding corroborates the fact that the significant difference observed in the number of times rescue analgesic was requested for between the various study groups in this present study was due to the addition of Vitamin C[32].

CONCLUSION: Demand for post-operative rescue analgesia due to moderate and severe pain was higher in participants who received analgesics alone regimen as opposed to their analgesics-adjuvant ascorbic acid regimen counterparts.

RECOMMENDATIONS

1. A multimodal analgesic regimen that incorporates intravenous Vitamin C after surgery may be a useful strategy for improving analgesia after caesarean section.

2. Multi-center clinical trials are needed to strengthen the evidence provided by this study.

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