Research Article

ISSN 2771-9057

Recent Advances in Clinical Trials

Oxytocin versus Oxytocin and Melatonin in Reduction of Blood Loss at Cesarean Section in a Resource Poor Setting, Southeast Nigeria: A Double Blinded Randomized Controlled Trial

Uchenna Nelson Nwaedu, Odidika Ugochukwu Joannes Umeora, Matthew Igwe Nwali*, Joshua Adeniyi Adebayo, Cosmas Ayadiuno Nnonyelu, Upo Emeri Mba, Joseph Agboeze, John Okafor EGEDE and Nnenna Assumpta Nweke

Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Ebonyi State, Nigeria.

***Correspondence:**

Nwali Matthew Igwe, Department of Obstetrics and Gynaecology, Alex Ekwueme Federal University teaching Hospital, PMB 102, Abakaliki, Ebonyi State 480001, Nigeria.

Received: 30 Nov 2023; **Accepted:** 03 Jan 2024; **Published:** 12 Jan 2024

Citation: Nwaedu UN, Umeora OUJ, Nwali MI, et al. Oxytocin versus Oxytocin and Melatonin in Reduction of Blood Loss at Cesarean Section in a Resource Poor Setting, Southeast Nigeria: A Double Blinded Randomized Controlled Trial. Recent Adv Clin Trials. 2024; 4(1); 1-11.

ABSTRACT

***Purpose**: Oxytocin is used to prevent hemorrhage due to uterine atony but postpartum hemorrhage is still a problem. Melatonin was suggested as an adjunct to oxytocin in blood loss reduction during cesarean. This study determines the effectiveness of Melatonin with oxytocin versus Oxytocin alone in reducing blood loss at cesarean section.*

***Methods**: A double blinded randomized controlled trial for cesarean section. One arm received 10mg of sublingual melatonin while the other arm received placebo (100mg of Vitamin C) after spinal Anesthesia. 10IU of intravenous Oxytocin was given to both arms after the delivery of the baby. The concept of intention to treat was used for protocol deviations during the study period.*

***Results:** Sociodemographic, indication and type of surgery were fairly distributed in the two arms. There was no significant difference in preoperative hemoglobin and platelet count. Blood loss was lower in melatonin arm ($P < 0.001$) and postoperative hemoglobin ($P = 0.003$). The placebo arm higher difference between preoperative and postoperative hemoglobin ($P < 0.001$) and received higher blood transfusion ($P = 0.049$). Side effects and neonatal outcome were same.*

***Conclusion**: Melatonin with oxytocin reduces blood loss during cesarean section more than oxytocin alone with minimal fetal and maternal side effects and should be encouraged.*

***Contribution:** Combination of sublingual melatonin and oxytocin reduces hemorrhage, blood transfusion and maternal mortality after cesarean section.*

Keywords

Oxytocin, Melatonin, Cesarean section, Blood loss.

Introduction

Postpartum hemorrhage is the leading cause of maternal mortality and contributes nearly one quarter of all maternal deaths globally [1]. Most deaths from postpartum hemorrhages occur within the first 24 hours of delivery [1]. In the United States in 2013, about 17.3 deaths per 100,000 live births were pregnancy-related and 11.4% of these deaths were due to postpartum hemorrhage

[2]. However, World health organization statistics suggests that 60% of maternal mortality in developing countries were due to postpartum hemorrhage [2]. Cesarean section is associated with severe hemorrhage. The risk of severe hemorrhage after cesarean section is twice the risk of severe hemorrhage after vaginal delivery [3]. A study done at Owerri South East Nigeria, found that cesarean section was associated with higher prevalence of postpartum hemorrhage (56.4%) [4]. In Abakaliki, Ebonyi State, a 10year retrospective study noted that 16.4% of deliveries were by cesarean section and a maternal mortality rate of 6.1% of which hemorrhage contributed to 44.2% of the maternal death [5]. The commonest cause of postpartum hemorrhage is uterine atony [3]. This risk of severe hemorrhage can be prevented by using uterotonic prophylactically to prevent uterine atony during cesarean section [6,7]. Oxytocin is popularly used as the first-line prophylactic uterotonic during cesarean section [8]. It is produced in the hypothalamus and stored by the posterior pituitary [9]. It can be released during sexual activities, pregnancy, uterine contraction, milk ejection, social bonding, and stress [9]. The mechanism of action of oxytocin involves the activation of oxytocin receptors, which triggers uterine contraction by elevating intracellular calcium ions [10]. Following parenteral administration, its effect on the uterus appears within 1-7 minutes and persists for 30 - 60 minutes [11]. It can be fraught with complications such as anaphylactic reactions, antiplatelet, antidiuretic, and negative inotropic effects especially in high doses [12]. It can equally be denatured by light thereby reducing its efficacy if the cold chain is not maintained [13]. For these reasons, an additional uterotonic may be required as an adjuvant therapeutic option for prevention of postpartum bleeding [14]. Melatonin is an N-acetyl-methoxy tryptamine originally used in the management of insomnia to improve sleep pattern [15]. It is an endocrine hormone released from the epithalamic portion of the pineal gland and commonly called sleep hormone. It has an anti-inflammatory, antioxidant and antiapoptotic characters and it has the tendency to influence the circadian rhythms and promotes fetal growth and neurogenesis by protecting ischemic process with no adverse fetal or neonatal outcomes recorded from its use [16]. The mechanism of action of melatonin is by binding to the specific G protein-coupled receptors, melatonin receptors (MT1 and MT2) that are distributed in the central nervous system [17]. The activation of the different melatonin receptors in humans slows the blood flow to the assorted vascular beds. Melatonin has been shown to have anxiolytic effect and is effective in the management of surgical and inflammatory pains [18]. It is mainly produced at night by the pineal gland in a circadian manner. It plays a vital role in uterine physiology with the tendency to initiate uterine contraction in pregnancy [19,20]. Study has shown that melatonin levels increase in maternal blood, amniotic fluid and in the urine of pregnant women in all stages of pregnancy and peaks at term while it is reduced by factors such as smoking, stress, aging and exposure to excessive lights [21]. It has a half-life of forty to sixty minutes with plasma peak concentration of four to five hours after the onset of action and metabolized in the liver and kidneys [22]. Melatonin prevents blood loss by enhancing oxytocin activity thereby promoting myometrial cell contractions, which in turn prevent uterine atony [23]. Another mechanism of blood loss reduction by melatonin is by its anxiolytic effect that causes reduction of anxiety and fear which in turn prevents elevated blood pressure that would have led to excessive hemorrhage [24]. Combined treatment of melatonin and oxytocin could result in a two-fold increase in contractile response compared with oxytocin alone thereby preventing excessive blood loss at cesarean section which is achieved by synergistic promotion of coordinated and forceful uterine contraction [25].

Background

Melatonin use in prevention of blood loss during cesarean section may provide a cheap, easily administered alternative that is heat-stable with minimal or no allergic reaction to prevent postpartum hemorrhage and its attendant complications including maternal mortality. Its anxiolytic effects help prevent postoperative pains and equally improve the patient sleeping pattern. A single study done in Indian showed the efficacy of melatonin combined with oxytocin in reduction of blood loss at cesarean section [18]. Cesarean section can be complicated by severe bleeding, resulting from uterine atony. Other causes of undue bleeding include abnormal placentation, trauma, previous cesarean section and sepsis [26]. This can be effectively managed with the use of oxytocic which ensures uterine contractility. The cesarean section rate in Nigeria is 3% [27,28]. A cross sectional study in South Africa noted that about one in 216 cases of cesarean section were complicated by severe morbidities from bleeding, of which about one in 14 women with severe morbidity will end up as maternal mortality [29]. It was noted that women on low dose oxytocin required additional oxytocic. This study concluded with the recommendation that administration of additional uterotonic to oxytocin bolus after cesarean section should be advocated [30]. A study in USA on the transcriptional regulation of melatonin receptor expression in human myometrial cells using late term pregnant volunteers, concluded that circulating melatonin plays a significant role in the timing and degree of uterine contraction in late-term pregnancy with possible reduction in blood loss from myometrial contraction [31]

Objectives

Oxytocin has been shown to reduce blood loss at Cesarean section. However, addition of other drugs makes it more effective. Some adjuncts studied, include tranexamic acid but was administered intravenously, this might be difficult in a population like Nigeria where less than 40% of deliveries are attended by traditional birth attendants [32]. Misoprostol has been used but is associated with fever, nausea, chills, and rigor. Melatonin also plays its part in reducing blood loss. Its anxiolytic properties may help in improving postoperative condition. There is a limited publication on melatonin use in reduction of blood loss at cesarean section. The study done that compared oxytocin and melatonin versus oxytocin alone was in India. It is therefore necessary that more work be done to assess the effectiveness of melatonin in reduction of blood loss at cesarean section among the local population of women in Abakaliki, Southeast Nigeria. Hence, the reason for

the study to know if it is effective in Africa especially Nigeria. It therefore merits to be evaluated as no similar study within the limits of our search has been conducted in Southeast Nigeria. Primary postpartum hemorrhage is the commonest cause of maternal mortality in Nigeria [4,33]. Its commonest cause is uterine atony while oxytocin is the drug of choice for its prevention and management when it occurs. However, despite the use of oxytocin over the years, hemorrhage still accounts for significant morbidity and mortality during or after cesarean section. As a result of this, other agents such as misoprostol and ergometrine are sometimes used as adjunct in prevention and management of primary postpartum hemorrhage. These drugs are however contraindicated in some categories of people, thus preventing their universal application like oxytocin. Melatonin, which is heat stable may be helpful as an adjunct to support oxytocin in its role of prevention of postpartum hemorrhage. It is cheap, readily available and can equally be administered orally or sublingually. It can be used in patients with asthma where misoprostol is contraindicated and also in hypertensive and heart failure patients where ergometrine is contraindicated. These attributes therefore, favor the use of melatonin in rural setting and by low cadre health care workers. It is equally used in the treatment of sleeping disorder and its anxiolytics properties improve patients' conditions by preventing postoperative pains which oxytocin lacks. Few studies have been done in Africa comparing melatonin and oxytocin versus oxytocin alone. Thus, the need for this study using 10mg of sublingual melatonin among pregnant women undergoing cesarean section in Abakaliki.

Materials and Methods

Theory

The study was a superiority double-blind randomized controlled trial That lasted for five months, from 1st November, 2021 to 30th March, 2022. Abakaliki is the capital of Ebonyi state in Southeast Nigeria. It has a population of about 438,700 [34]. They are mainly peasant farmers, traders, civil servants, politicians and students. Pregnant women in the area tend to avoid cesarean sections for socio-cultural reasons and fear of complications [35]. There is high aversion for blood donation and transfusion [36]. The Teaching Hospital caters for both primary and referred cases from Ebonyi and neighboring states. Patients are booked for antenatal care in the hospital while patients that are referred from elsewhere due to pregnancy or delivery complications are regarded as unbooked. The antenatal women are seen based on scheduled appointments and those who require admission are admitted into the antenatal ward. Unpublished report showed that the total number of deliveries in 2020 was 2062; 874 were via cesarean section. The study population included women selected for either elective or emergency caesarean section at term who met the inclusion criteria and consented to the study. Inclusion criteria 1. Women with term pregnancy, 2. Women that consented to the study, 3. Women booked for both elective and emergency cesarean sections. Exclusion criteria 1. Patients with documented bleeding disorders, 2. Acute obstetric emergency, 3. Medical diseases in pregnancy such as cardiac disease, or hemoglobinopathies, 4. Antepartum hemorrhage, 5. Previous uterine rupture, 6. Women with co-existing uterine pathology e.g. fibroids and 7. Those that refused consent.

Departmental Protocol for Caesarean Section

Cesarean sections are carried out in the obstetrics theatre after due preoperative preparation. Informed written consent is obtained from the patients. Majority are performed under regional anesthesia. Entry into the peritoneum is gained via a sub umbilical midline or Pfannenstiel incision depending on the indication for the surgery. The uterus is opened via a lower uterine segment transverse incision after correcting for any uterine rotation. Care is taken not to injure the bladder. Thereafter the baby is gently delivered manually or with the use of Wrigley's forceps. The umbilical cord is clamped in two places and divided in between and baby handed over to the pediatrician. Parenteral oxytocin is given. The placenta and membranes are delivered by cord traction and the uterine cavity is cleaned with sterile gauze. Uterine and abdominal incisions are closed in layers after securing hemostasis. The lower genital tract is inspected, clots expelled and a pad inserted. The abdominal wound is dressed and covered. Patients with excess blood loss or primary postpartum hemorrhage were given additional oxytocic, tranexamic acid and blood transfusion.

Sample size Calculation

The sample size was calculated using the formula for a clinical superiority randomized controlled trial (continuous variables) [37].

$$N = \frac{2 \times (Z1\text{-}\alpha + Z1\text{-}\beta)^2 \times S^2}{(d - d0)}$$

Where N= sample size for each group,
Z =standard normal deviate for a one- or two-sided x,
d = the real difference between two treatment effect
d0 = a clinically accepted margin
S^2 = polled standard deviation of both comparison groups
Substituting for,
$Z1\text{-}\alpha = 1.645$ (where $\alpha = 0.05$)
$Z1\text{-}\beta = 0.845$ (where $\beta = 0.20$)
d0 =0.58 (according to Khezri et al.) [18]
d =0.15 (Khezri et al.) [18]
Substituting,

$$N = 2 \times \frac{(1.645 + 0.845)^2 \times (1.31)^2}{(0.15\text{-}0.58)}$$

$$N = 2 \times \frac{(2.49)2 \times 1.7161}{(-0.43)}$$

N=2 x (-5.791)2 x 1.7161
N=2 x 33.535x 1.761
N= 115.1
Adding attrition (10%) = 115/10= 11.5 N= 115 +11.5 =126.5 N≅ 127 N= 127per arm

Recruitment of patients/Randomization and concealment

Patient who met the inclusion criteria without any exclusion factors and have been adequately educated, counselled and signed

the informed consent form were recruited and enrolled into the study. The participants were randomized by means of computer-generated random numbers by a Statician, using the software research randomizer. From the pool of numbers 1 to 254 inserted into the software, 127 numbers were randomly generated and assigned to Group 'A' (Melatonin plus Oxytocin group), while the remaining 127 numbers were automatically assigned Group B (placebo plus Oxytocin group). The numbers generated (1-254) were inscribed on brown envelopes and pieces of paper, which also had inscription 'A' or 'B' on them according to the group the number belonged. The pieces of paper were then inserted into the corresponding envelopes and arranged serially. These were then sent to the pharmacist who packaged the drugs in the envelopes according to the groups as labelled 'A' and 'B' and subsequently sealed them. Group A received 10mg of sublingual melatonin one minute after induction of spinal Anesthesia and 10IU of intravenous Oxytocin after the delivery of the baby. Group B receive sublingual 100mg of Vitamin C one minute after induction of spinal Anesthesia and 10IU of intravenous Oxytocin after the delivery of the baby. Concealment was done in sequentially numbered sealed envelopes. The numbers 1-254 were inscribed on brown sealed envelopes. These were brought in batches as needed for the study. The concealment was done by the hospital Pharmacist who was not part of the study. All the envelopes were kept in the theatre inside a locker accessible to all members of the research team. Contents of each envelop were administered sequentially to the participants as they present for Cesarean section by the researcher or any of his assistants. Both drugs appear similar and hence the patients, investigators as well as the Anesthetist did not know what drugs they got. The sequentially numbered envelopes 1-254 released in batches were kept in the theatre Pharmacy inside a locker designated for the drugs. Each envelope contained either 10mg of Melatonin tablet or 100mg of Vitamin C tablet (placebo) as randomized above. Both the Melatonin and Vitamin C were white in color and of the same shape and size. The Participants received a single dose of either Melatonin or Vitamin C (placebo) after one minute of the administration of spinal anesthesia. Pre-operative hemoglobin and platelet count of the participants were done not more than two days before the surgery. The surgeries were performed by either a Consultant or a senior Registrar. Participants were closely observed throughout the period of the surgery for any adverse effects but none was detected. The spinal anesthesia was administered by a senior Registrar in Anesthesia. All the groups were given intravenous oxytocin of 10IU immediately the baby was delivered. The APGAR scores of the babies on delivery were documented for fetal wellbeing. Precautionary measures were made for the immediate treatment of any undue side effects. The immediate postoperative condition was monitored by the research assistant in the recovery room for at least two hours before transferring patient to the ward. Hemodynamic status, adverse effects such as pruritus, dizziness, bradycardia, hypotension, and postoperative nausea and vomiting of the participant were assessed by the researcher and the research assistants. The vitamin C tablets and Oxytocin ampoules (Rotex brand) used for this study were procured from reputable pharmacy outlets. The batch numbers, expiring and manufacturing dates were noted and were valid throughout the period of the study. The Oxytocin ampoules were stored in a refrigerator at the temperature range of 20 to 80C. 22 Melatonin is marketed in the United States of America as supplements and not drugs. The brand (Member's mark from Sam's club US) used for the study was procured from the Sam's club outlet in Jonesboro AR 72401. USA. Its expiration date was on July 2022 while the study ended on March 2022.

Outcome measures

The primary outcome measures were the estimated blood loss at surgery and the level of drop in the mother's hemoglobin after forty-eight hours of surgery. The secondary outcome measures were development of primary postpartum hemorrhage, need for rescue drugs and blood transfusion.

Estimation of blood loss

The blood loss during and after cesarean section in this study was estimated using visual, gravimetric and difference in hemoglobin after 48 hours of surgery as thus: After surgery, blood on the floor, surgeon's and assistant's boots were estimated visually and recorded. Also, within the first six hours post-surgery, blood spill on the bed spread and mackintosh was visually estimated and recorded. Mops, delivery mat, Surgeons gown and drapes were pre-weighed before being used for surgery. These were weighed at the end of the surgery using spring balance weighing scale. The results were obtained by subtracting the weights before surgery from the weight post-surgery and the difference recorded in gram. Also, the vulva pads were pre-weighed 21 and re-weighed after use for the first six hours post-surgery and the difference in weight calculated and recorded in gram This was converted to milliliters using the ratio 1:1 (gram to milliliter). Postoperative hemoglobin was estimated 48hours after cesarean section. This was subtracted from the pre-operative hemoglobin and the difference recorded.

Data collection/Analysis

All data sheets were collected by the researcher. At the end of the study, the sheets were separated; and using the record of randomization sequence, the label of the envelopes were sorted out according to the participants and their data in the appropriate groups. The data were analyzed using IBM SPSS (version 25.0; Chicago IL, USA, August 2017) and by the concept of intention to treat and taken care of protocol deviations during the study period. Absolute and relative frequencies of categorical variables, mean and standard deviation of continuous variables were calculated. Continuous variables were analyzed by t-test, $\chi 2$ test were used for categorical variables while comparison of two mean were done using the t-test. P-value of 0.05 or less were taken as significant.

Ethical Issues

Ethical clearance was obtained from the research and ethics committee of the Hospital. All the participants were adequately educated, counselled and signed the informed consent form before recruitment. Participants that had excess blood loss or primary postpartum hemorrhage were managed according to

the departmental protocols. The participants and their babies were followed up closely till 48 hours after surgery when the participants' postoperative hemoglobin was determined. Anemic participants were given hematinics while some were transfused, depending on the severity of the anemia. All information about the patient were kept strictly confidential. All the financial implications of this study were borne by the researchers. The clinical trial was registered with ID: PACTR 2022018386453.

Results

Three hundred and sixteen (316) pregnant women were assessed for eligibility. Out of the 316 women, fifty-nine, (59) were excluded while two hundred and fifty-four 254 participated fully in the study as shown in the study flow chart (figure 1). Table 1 shows the socio-demographic/obstetrics characteristics of the participants. The mean age was 29.5 ±5.8 years and 30.2 ± 6.0 for melatonin and placebo arms respectively. The mean parity was 2.9 ±1.7 and 2.9 ±1.6 for Melatonin and placebo arms respectively while mean gestational age was 39.0 ±2.1 for melatonin arm and 38.6 ±2.3 for placebo arm. This showed no significant difference in any of the parameters between the two study groups. Table 2 shows the indications for cesarean section. The differences between the indications were not statistically significant. Table 3 showed the types of cesarean section undergone by the participants. The difference in primary and secondary cesarean section on both arms as well as the difference in elective and emergency cesarean sections were not statistically significant. Table 4a showed the units of blood transfused versus cesarean section indications in the two study arms. There was no statistical difference in the units of blood transfused per indication in the two arms of the study. Table 4b shows the summary of the units of blood received by the participants. More participants were transfused in the control group as compared to the study group. The difference in blood transfusion between women who received one unit, as well as those who received two units of blood, was statistically significant (P-value = 0.019 and 0.049 respectively). Table 5a shows mean estimated blood loss based on indications for cesarean section and are statistically significant for prolonged labor, fetal related factors and maternal medical conditions. For all these indications, blood loss was significantly higher among women who received oxytocin alone as compared with those who received oxytocin and melatonin across other indications. Table 5b shows estimated blood loss in both groups. Participants in the control group (oxytocin only) lost more blood than those in the study group (Melatonin + oxytocin). The difference in estimated blood loss between the two groups was statistically significant. Table 6 compared the blood loss between the study and control groups. There was no significant difference in pre-operative platelet and pre-operative hemoglobin count; whereas there were significant differences in post-operative hemoglobin, difference in hemoglobin, estimated blood loss at surgery and blood transfusion at surgery in the two study groups. Table 7 showed the comparison of the side effects of the drugs between the two groups. There was no significant difference between the two groups in the side effects of the drugs used for the study. Table 8, showed Neonatal outcome, the APGAR Scores on the 1st and 5th minutes. The APGAR scores of the neonates on both arms as well as newborn admission showed no significant difference statistically.

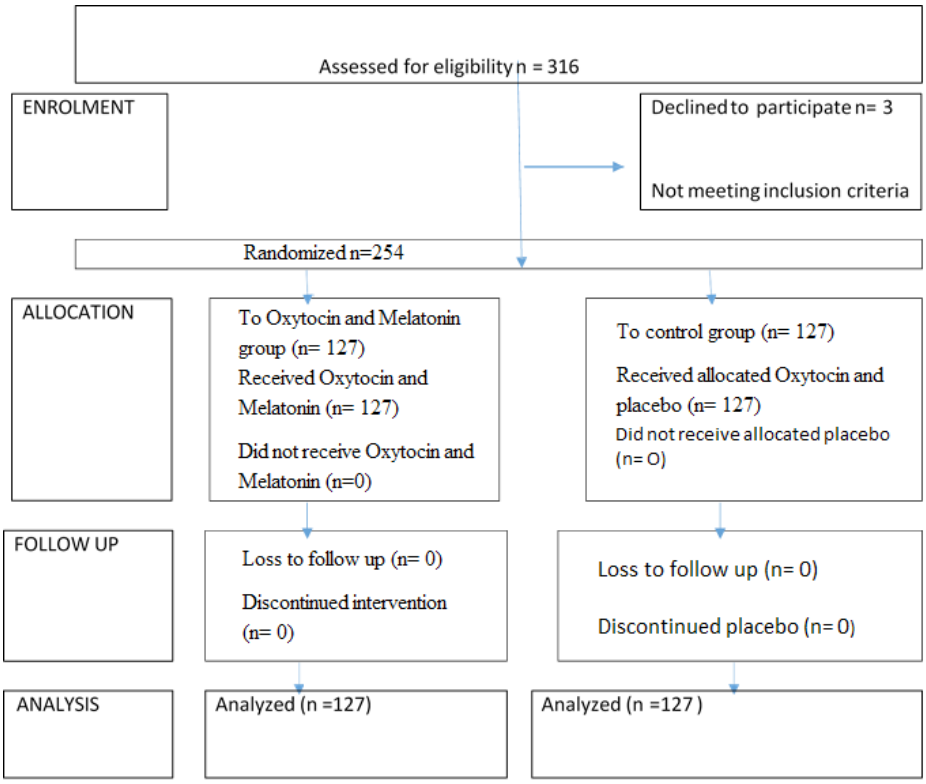

Figure 1: Consort Diagram.

Table 1: Socio-demographic data of participants.

Socio-demographic Data	Melatonin Group	Control Groupe	χ^2	P-valu
	(n=127)	(n=127)		
Age (years)				
15-19	7 (5.5%)	8 (6.3%)	4.148	0.528
20-24	17(13.4%)	14(11.0%)		
25-29	36(28.3%)	32(25.2%)		
30-34	39(30.7%)	33(26.0%)		
35-39	22(17.3%)	35(27.6%)		
40-44	6 (4.7%)	5 (3.9%)		
Mean (±SD)	29.5 (±5.8)	30.2 (±6.0)		
Parity				
0	13(10.2%)	11 (8.7%)	0.237	0.888
1–4	90(70.9%)	93(73.2%)		
≥5	24(18.9%)	23(18.1%)		
Gestational age (weeks)				
37–<39	47(37.0%)	51(40.2%)	1.594	0.451
39–<41	51(40.2%)	55(43.3%)		
Mean (±SD)	39.0 (±2.1)	38.6 (±2.3)		
Occupation				
Trader	29(22.8%)	47(37.0%)	9.583	0.143
Civil servant	29(22.8%)	17(13.4%)		
Farmer	19(15.0%)	18(14.2%)		
Students	17(13.4%)	11 (8.7%)		
Seamstress	8 (6.3%)	10 (7.9%)		
Housewife	10 (7.9%)	7 (5.5%)		
Others	15(11.8%)	17(13.4%)		
Religion				
Christianity	121(95.3%)	119(93.7%)	1.430*	0.694
Muslim	2 (1.6%)	5 (3.9%)		
African Traditional Religion	4 (3.1%)	3 (2.4%)		
Marital status				
Married	106(83.5%)	104(81.9%)	0.617*	0.923
Unmarried	15(11.8%)	17(13.4%)		
Divorced	3 (2.4%)	4 (3.1%)		
Widowed	3 (2.4%)	2 (1.6%)		
Booking status				
Booked	83(65.4%)	80(63.0%)	0.154	0.695
Unbooked	44(34.6%)	47(37.0%)		
Residence				
Urban	74(58.3%)	71(55.9%)	0.145	0.704
Rural	53(41.7%)	56(44.1%)		

Table 2: Indications for Cesarean Section.

Indications	Melatonin + Oxytocin	Oxytocin only	Total	χ2	p-value
	n (%)	n (%)	n (%)		
Obstructed labor/CPD	45 (35.4)	37 (29.1)	82 (32.3)	1.15	0.283
Failed IOL/AOL due to cervical dystocia	11 (8.7)	5 (3.9)	16 (6.3)	2.40	0.121
Previous CS with PROM/twin gestation	13 (10.2)	13 (10.1)	26 (10.2)	0.00	1.000
Malpresentation	28 (22.0)	26 (20.5)	54 (21.3)	0.09	0.759
Maternal medical conditions	23 (18.1)	32 (25.2)	55 (21.7)	1.88	0.170
Postdate with abnormal BPP	7 (5.5)	14 (11.0)	21 (8.3)	2.54	0.171
Total	**127 (100.0)**	**127 (100.0)**	**254(100)**		

Table 3: Types of Cesarean Section.

Type of Cesarean	Melatonin + Oxytocin	Oxytocin only	Total (%)	χ2	P-value
Section	**n=127 (%)**	**n=127 (%)**			
Primary	96(53.3)	84(46.7%)	180(70.9)	2.754	0.096
Secondary	31(41.9)	43(58.1)	74 (29.1)		
Elective	76(55.1)	62(44.9)	138(54.3)	3.111	0.078
Emergency	51(44.0)	65(56.0)	116(45.7)		

Table 4a: The units of blood transfused versus cesarean section indications in the two study arms.

Variables	Units of Blood Transfused			
	Melatonin + Oxytocin	**Oxytocin Only**		
	n (%)	**n (%)**	**χ2**	p-value
Indication for Cesarean section				
Obstructed labor/CPD	5 (33.3)	7 (25.9)	1.87	0.172
Failed IOL/AOL due to cervical dystocia	2 (13.3)	3 (11.1)	FT	0.776
Previous CS with PROM/twin gestation	2 (13.3)	5 (18.5)	FT	1.000
Malpresentation	2 (13.3)	4 (14.8)	FT	0.893
Maternal medical conditions	2 (13.3)	3 (11.1)	FT	0.831
Postdate with abnormal BPP	2 (13.3)	5 (18.5)	FT	0.666
Total	15 (100.0)	27 (100.0)	4.108	0.043

FT =Fisher's exact test

Table 4b: Units of blood transfused on each arm.

Units of Blood Transfused	**Melatonin + oxytocin**	**Oxytocin**	**Total**	**χ2**	**p-value**
1	15(44.1%)	19(55.9%)	34(81.0%)	5.49	0.019
2	0 (0.0%)	6(100.0%)	6 (14.3%)	3.89*	0.049
4	0 (0.0%)	2(100.0%)	2 (4.7%)	1.17*	0.280
Total	**15(35.7%)**	**27(64.3%)**	**42(100%)**	**4.108**	**0.043**

*Fisher exact test used

Table 5a: Mean Estimated blood loss versus cesarean section indications.

Indications for cesarean section	**Melatonin + Oxytocin**		**Oxytocin only**		**t-test**	**p-value**
	N	**Mean ±SD**	***N***	**Mean ±SD**		
Obstructed labor/CPD	45	441.33±103.78	37	629.73±181.61	-5.60	<0.001
Failed IOL/AOL due to cervical dystocia	11	409.09±66.40	5	471.05±132.62	-0.99	0.644
Previous CS with PROM/twin gestation	13	476.92±166.60	13	857.69±603.75	-2.19	0.056
Malpresentation	28	415.71±44.67	26	692.31±230.08	-6.025	<0.001
Maternal medical conditions	23	517.39±161.39	32	743.75±431.75	-2.71	0.013
Postdate with abnormal BPP	7	435.71±80.18	14	514.29±154.96	1.53	0.25
Total	**127**	**450.00±115.60**	**127**	**704.33±348.18**	**7.812**	**<0.001**

Table 5b: Summary of estimated blood loss at cesarean section.

Estimated Blood Loss (ml)	**Melatonin + Oxytocin**	**Oxytocin only**	**χ2**	**P-value**
<500	79(75.2%)	26(24.8%)	45.60	<0.001
500-<1000	42(33.1%)	85(66.9%)	29.12	<0.001
>1000	6 (27.3%)	16(72.3%)	4.98	0.026

Table 6: Preoperative hemoglobin, platelet and comparison of blood loss.

Blood Loss	**Melatonin Group (n=127)**	**Control Group (n=127)**	**t-test**	**P-value**
Pre-operative platelet count	326.48±28.70	326.33±28.544	0.042	0.967
Pre-operative Hemoglobin	10.45±1.13	10.53±0.98	0.588	0.557
Post-operative Hemoglobin	9.57±0.96	9.21±0.93	2.965	0.003
Difference in Hemoglobin (Preop – Postop Hemoglobin)	0.88±1.10	1.32±0.83	3.566	<0.001
Estimated blood loss at Surgery	450.00±115.70	704.33±384.18	7.812	<0.001
Blood transfusion at surgery	1.00±0.00	1.44±0.85	2.022	0.049

Table 7: Comparison of drug side effects.

Side Effects	**Melatonin Group**	**Control Group**	χ^2	**P-value**
	(n=127)	**(n=127)**		
Nausea	27(21.3%)	31(24.4%)	0.36	0.549
Drowsiness	7 (5.5%)	3 (2.4%)	1.67	0.197
Vomiting	4 (3.1%)	5 (3.9%)	0.12*	0.734
Hypotension	4 (3.1%)	2 (1.6%)	0.68*	0.409
Headache	0 (0.0%)	3 (2.4%)	3.06*	0.081
Bradycardia	0 (0.0%)	3 (2.4%)	3.06*	0.081

*Fisher's exact test used

Table 8: Neonatal outcome.

Data	Melatonin	Control Group	Test Statistic	P- value
	Group (n=127)	(n=127\	T-test / χ^2	
1ST Minutes APGAR	7.72±1.66	7.61±1.96	0.481*	<0.630
Score				
5th Minute APGAR	9.18±1.83	8.95±1.33	0.233*	0.253
Score				
Newborn admission Yes	12 (9.4%)	9 (7.1%)	0.467**	0.494
No	115(90.6%)	118(92.9%)		
* t-test used	** χ^2 test used			

Discussion

In this study, the socio-demographic and obstetric characteristics of the participants in the two arms were similar, as there was no statistically significant difference between the two groups of participants in the study. This is an indication that the participants were objectively distributed into the two arms of the study, thus reflecting the fairness of the randomization process and limiting bias. This therefore, makes the findings from the study good representations of the study population. In this study, the indications for cesarean section were similar in the two groups; there was no statistically significant difference in the indications for cesarean section between the two groups. This may reflect the effective randomization done to evenly distribute the participants into the two arms of the study. Similar studies did not review the indication for cesarean section in both arms of their studies [18,38]. Also, the difference between the participants who had primary and secondary cesarean sections as well as those who had elective and emergency cesarean sections did not show statistically significant difference, reemphasizing the fairness of the randomization process. The works reviewed for this study did not analyze the type of cesarean section done for participants [18,38]. The average estimated blood loss in this study was significantly lower among the participants in the melatonin group. The significantly lower blood loss in the melatonin group compared to the control group in this study supports the effects of melatonin on the uterine muscle, as an adjunct to uterotonics like oxytocin, in causing uterine contraction and achieving hemostasis. However, this was different from a previous study that found no significant difference in the blood loss between the group that received melatonin and the placebo [38]. This difference may be due to the smaller dosage (6mg) of the drug used in their study as against the higher dose (10mg) used in this study. This is an indication that higher doses of melatonin may be more effective than the lower doses in complementing the uterotonic activities of oxytocin, thereby significantly reducing blood loss associated with cesarean section. There were significant differences in the total units of blood transfused between the melatonin group and the control group, with more units of blood transfused to participants in the control group. The lower blood transfusion among the participants in the melatonin group correlated with smaller blood loss among them. This supports the synergistic effect of melatonin with oxytocin in reduction of blood loss at cesarean section. The previous studies did not review the quantity of blood transfused to participants in both groups [18,38]. The study showed that participants in both study arms had hemoglobin above 10g/dl pre-operatively; and there was no statistically significant difference in the pre-operative hemoglobin level between the two arms of the study. This could be due to the effectiveness of the randomization process. Participants in Jayashree et al. [38] study also had above 10g/dl on both sides of the study with no statistically significant difference in the pre-operative hemoglobin between the two arms of their study. The similarity with this study could be due to the fact that the current study employed similar patient recruitment and randomization processes as theirs. This finding however differed from the findings by Khezri et al., which showed significant difference in the pre-operative hemoglobin of the participants on both arms of their study [18]. This was possibly due to the fact that their study was divided into three arms as against the two arms of this study. Also, the preoperative platelet count of participants in this study was within normal range; and the difference between the two groups was not statistically significant. This implied that the participants recruited for this study on either side, did not have additional risks of bleeding tendencies as to affect the outcome of the study. Preoperative platelet count was not done to evaluate for background bleeding tendencies in the participants in the two previous studies reviewed. This may have had effect on the outcome of their studies. This study found that there was statistically significant difference in the post-operative hemoglobin as well as difference in hemoglobin before and after the surgery between the two groups. This was as a result of the increase in blood loss noticed in the control group when compared with the study group. This could be due to the uterotonic effect of melatonin when combined with oxytocin. This is similar to the findings in the study by Khezri et al. in the group that receive 6mg of melatonin. This is in contrast to the group that received 3mg of melatonin [18] and Jayashree et al. who found no significant difference between the melatonin and placebo groups in postoperative hemoglobin, difference in hemoglobin before and after surgery as well as the units of blood transfused. This difference in the findings may be due to the smaller sample sizes employed by the two studies as compared to the current one as well as smaller doses (3mg and 6mg) of melatonin used in their studies, which might not have had as much effect as the higher dose used in this study. This study showed no significant difference in the observed side effects such as nausea, drowsiness, vomiting, hypotension, headache and bradycardia between the two groups. The non-significant finding in nausea and vomiting is likely due to the sublingual administration of the melatonin. This avoids direct impact of the drugs on the gastrointestinal tract. This was similar to the finding by Jayashree et al. who also observed no significant difference in the listed complications despite the

difference in the dosage used in the two studies [38]. This was possibly as a result of similar route of administration employed in both studies. This was however different from the findings by Khezri et al. who found a significant difference in headache in the melatonin group that received higher dose (6mg). They attributed this to melatonin exaggerating the intracranial hypotension induced by the Dural puncture in those who had spinal anesthesia [18]. The side effects found in this study may be attributed to the oxytocin received in both arms as melatonin causes more of CNS side effect. The hypotension observed more in the melatonin group can be expressed as the role of melatonin in the reduction of blood pressure as shown by Langston Cox et al. [39]. This was also supported by the study done by Marseglia et al., which equally demonstrated peri-operative hypotensive effect of melatonin [40]. This effect may be due to the anxiolytic and sedative properties of melatonin as demonstrated in a study by Yousaf et al. and Ismali et al. [41,42]. There was no headache among the participants in the melatonin group as compared to the control group in which three participants developed headache, though the difference was not statistically significant. The absence of headache in the study group may be due to the analgesic effect of melatonin as found by Khezri in his study on analgesic effect of melatonin in patients who underwent cesarean section [43]. The difference in the first- and fifth-minutes APGAR scores and neonatal admissions between the melatonin and control groups in this study, was not statistically significant. This is due to the fact that melatonin, given as a single dose and for short duration before the delivery of the baby, is not known to have any adverse effect on the newborn [44]. This was similar to the finding by Khezri et al. who found no significant difference in fetal outcome between the study and control groups [18]. This corroborates the fact that single dose of melatonin has no adverse effect either on the fetus during labor or on the newborn after delivery.

Conclusion

This study showed significant difference in post-operative hemoglobin; difference between preoperative and post-operative hemoglobin, blood loss as well as the unit of blood transfused during cesarean section between the study group and the control group. There was no significant difference in the maternal and neonatal side effects among the participants in this study. Thus, melatonin with oxytocin reduces blood loss during cesarean section more than oxytocin alone with minimal fetal and maternal side effects and should be encouraged.

Limitations of the study

This was a single center study; and a multi-center study may be necessary for a more robust conclusion on melatonin efficacy in blood loss reduction at cesarean section. It was not easy to avoid liquor from mixing with blood in using mops, though this would cancel out between the two groups. This might have affected the total weight and ultimately the estimated blood loss. Also, visual blood loss estimation is subjective and lacks accuracy as it is based on Surgeon and Anesthetist assessment.

Strength/Contribution to knowledge

This study is a randomized controlled trial; and double blinding was done to prevent bias. This work will contribute to the knowledge of reduction of post- partum hemorrhage, which is one of the major complications of cesarean section thereby reducing maternal mortality.

Acknowledgement

We are very grateful to the research and ethics committee of the Teaching Hospital, for approving this study protocol. We also wish to express our profound gratitude to the staff of the Anesthesiology and Obstetrics/Gynecology units, for their assistance in providing the necessary procedures for this study as well as our research assistants who helped us in data collection. We are also grateful to the Pharmacology unit who helped to procure and package the drugs appropriately for the study.

References

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death a WHO systematic analysis. Lancet Glob Health. 2014; 2: 323-333.
2. Smith JR. Postpartum Hemorrhage. Medscape. 2018. https://emedicine.medscape.com/article/275038-overview.
3. Rossen J, Okland I, Nilsen OB, et al. Is there an increase of postpartum hemorrhage and is severe hemorrhage associated with more frequent use of obstetric interventions. Acta Obstet Gynecol. 2010; 89: 1248-1255.
4. Onyema OA, Cornelius AC, Uchenna ET, et al. Primary postpartum haemorrhage in Federal Medical Centre Owerri Nigeria A sixyear review. Niger J med. 2015; 24: 242-245.
5. Onoh RC, Eze JN, Ezeonu PO, et al. A 10yearappreciall of caesarean delivery and the associated fetal and maternal outcomes at a teaching hospital in south east Nigeria. Int J women health. 2015; 7: 531-538.
6. KellieFJ. Medical methods for preventing blood loss at caesarean section. Cochrane Database Syst Rev. 2018; 2018: CD007576.
7. Halder S, Samanta B, Sardar R, et al. Tranexamic acid used before caesarean section reduces blood loss based on pre and postoperative haemoglobin level A case-control study. J Indian Med Assoc. 2013; 111: 184-186.
8. Parry smith WR, Papadopoulou A, Thomas E, et al. Uterotonic agents for first-line treatment of postpartum haemorrhage a network meta-analysis. Cochcrane database of syst rev. 2020; 11: CD012754.
9. Magon N, Kalra S. The orgasmic history of oxytocin love lust and labour. Indian J endocrinolmetab. 2011; 15: 156-161.
10. Arrowsmith S, Wray S. Oxytocin its mechanism of action and receptor signaling in the myometrium. J Neuroendocrinol. 2014; 26: 356-369.
11. Adnan N, Conlan-Trant R, McCormick C, et al. Intramuscular oxytocin versus intraveinous oxytocin to prevent postpartum

haemorrhage at vaginal delivery randomisized controlled trial. Brit Med J. 2018; 362: k3546.

12. Pant D, Vohra VK, Pandey SS, et al. Pulseless electrical activity during caesarean delivery under spinal anaesthesia a case report of severe anaphylactic reaction to syntocinon. Int J Obstet Anesth. 2009; 18: 85-88.
13. Mozziconacci O, Schoneich C. Photodegradation of oxytocin and thermal stability of photo products. J pharm sci. 2012; 101: 3331-3346.
14. Pakniat H, Khezri MB. The effect of combined oxytocin-misoprostol versus oxytocin and misoprostol alone in reducing blood loss at cesarean delivery a prospective randomized double-blind study. J Obstet Gynecol. 2015; 65: 376-381.
15. Amaral FG, Do Cipolla-Neto J. A brief review about melatonin a pineal hormone. Arch Endocrinol Metab. 2018; 62: 472-479.
16. Nagai R, Watanabe K, Wakatsuki A, et al. Melatonin preserves fetal growth in rats by protecting against ischemia reperfusion-induced oxidative nitrosative mitochondrial damage in the placenta. J Pineal Res. 2008; 45: 271-276.
17. Dubocovich ML, MarkowskaM. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine. 2005; 27: 101-110.
18. Khezri MB, Reihany MD, Dabbaghi G, et al. Effects of Melatonin on Blood loss after caesarean section A Prospective randomized double blind trial. J Obstet Gynaecol. 2019; 69: 436-443.
19. Tamura H, Nkamura Y, Terron MP, et al. Melatonin and pregnancy in the human review. Reprodtoxicol. 2008; 25: 291-303.
20. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med Rev. 2005; 9: 11-24.
21. Tenorio FD, Simões MDJ, Teixeira VW. Effects of melatonin and prolactin in prolactin in reproduction review of literature. Rev Assoc Med Bras. 2015; 61: 269-274.
22. Chattoraj A, Liu T, Zhang LS, et al. Melatonin formation in mammals in vivo perspectives. Rev Endocr metab disord. 2009; 10: 237-243.
23. Sharkey JT, Cable C, Olcese J. Melatonin sensitizes human myometrial cells to oxytocin in a protein kinase Cα extracellular-signal regulated kinase-dependent manner. J Clinendocrinolmetab. 2010; 95: 2902-2908.
24. Abdeshahi SK, Hashemipour MA, Mesgarzadeh V, et al. Effect of hypnosis on induction of local anaesthesia pain perception control of haemorrhage and anxiety during extraction of third molars a case control study. J Craniomaxillofac Surg. 2013; 41: 310-315.
25. Sharkey JT, Puttaramu R, Word RA, et al. Melatonin synergizes with oxytocin to enhance contractility of human myometrial smooth muscle cells. J Clinendocrinolmetab. 2009; 94: 421-427.
26. Fawcus S, Moodley J. postpartum haemorrhage associated with caesarean section and caesarean hysterectomy. Best pract Res clinobstet Gynaecol. 2013; 27: 233-2497.
27. Adewuyi EO, Auta A, Khanal V, et al. Caesarean delivery in Nigeria prevalence and associated factors a population based cross section study. Brit Med J open. 2019; 9: e027273.
28. Isah AD, Adewole N, Zaman J. A five-year survey of cesarean delivery at a Nigerian tertiary hospital. Trop J Obstet Gynaecol. 2018; 35: 14-17.

Maswime S, Buchmann EJ. Why women bleed and how they are saved a cross-sectionaal study of a caesarean section near-miss morbidity. BMC Pregnancy childbirth. 2017; 17: 15.

29. Munn MB, Owen J, Vincent R, et al. Comparison of two oxytocin regimens to prevent uterine atony at caesarean delivery a randomized control trial. Obstet Gynecol. 2001; 98: 386-390.
30. Martennson LGE, Andersson RGG, Berg G. Melatonin with noradrenaline arguments contractions of human myometrium. Eur J pharm. 1996; 316: 273-275.
31. Sulayman H, Adaji S. Integration of traditional birth attendants TBAs into the health sectors for improving maternal health in Nigeria a systematic review. Sub Saharan Afr J Med. 2019; 6: 55-62.
32. Ajenifuja KO, Adepiti CA, Ogunniyi, et al. Postpartum haemorrhage in a teaching hospital in Nigeria A 5-year experience. Afr Health Sci. 2010; 10: 71-74.
33. National Population commission. 2006 population and Housing Census of the Federal republic of Nigeria. Off Gaz Fed Repub Niger. 2009; 96.
34. Lawani LO, Igboke FN, Ukaegbe CI, et al. Perception and socio-cultural barriers to the acceptance of Caesarean delivery in a Tertiary hospital in Abakaliki south East Nigeria. Inter J Women's Health Reprod Sci. 2019; 7: 163-168.
35. Umeora OUJ, Onuh SO, Umeora MC. Socio-cultural barriers to voluntary blood donation for obstetric use in a rural Nigerian village. Afr J Reprod Health. 2005; 9: 72-76.
36. Zhong B. How to calculate sample size in randomized controlled trial. J Thorac Dis. 2009; 1: 51-54.
37. Jayashree V, Vanathi R, Baby M. Effects of melatonin in reducing blood loss during and after caesarean section. Inter J of Clinical Obstet and Gynecol. 2021; 5: 227-231.
38. Langston-Cox A, Marshal S, Lu D, et al. Melatonin for the management of Preeclampsia A Review. Antioxidant. 2021; 10: 376.
39. Marseglia LD, Angelo G, Manti S, et al. Potential utility of Melatonin in Preeclampsia Intrauterine Growth RetardationandPerinal Asphyxia. Reprod Sci. 2016; 23: 970-977.
40. Yousaf F, Seet E, Venkatraghavan L, et al. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period a qualitative systematic review of randomized trials. Anesthiology. 2010; 113: 968-976.
41. Ismail SA, Mowafi HA. Melatonin provides anxiolysis enhances analgesia decreases intraocular pressure and promotes better operating conditions during cataract surgery under topical anesthesia. Anesth Analg. 2009; 108: 1146-1151.

42. Khezri MB, Reihany MD, Oveisy S, et al. Evaluation of the Analgesic Efficacy of Melatonin in Patients undergoing cesarean Section under spinal Anesthesia A prospective randomized double-blind study**.** Iran J Pharm Res. 2016; 15: 963-971.

43. Chen Y, Tain Y, Sheen J, et al. Melatonin utility in neonates and children. J fma. 2012; 111: 57-66.