



A Randomised Controlled Trial on the Effectiveness of Melatonin in Controlling Blood Loss during Ceaserean Section in a Tertiary Centre in Southeast Nigeria

Chinomnso Stella MARCEL-ONWUDIWE ^a,
Odidika Ugochukwu Joannes UMEORA ^a,
Joshua Adeniyi ADEBAYO ^a,
Darlington-Peter Chibuzor UGOJI ^{b*},
Ifeoma Cecilia UCHE-OMOVOH ^a,
Emmanuel Chijioke UWAKWE ^a, Paschal Chijioke OKOYE ^b
and Enemma Christian ENEMMA ^a

^a Department of Obstetrics and Gynaecology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Ebonyi State, Nigeria.

^b Department of Obstetrics and Gynaecology, David Umahi Federal University Teaching Hospital, Uburu, Ebonyi State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: <https://doi.org/10.9734/ajmah/2025/v23i11165>

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/128846>

Original Research Article

Received: 02/11/2024
Accepted: 04/01/2025
Published: 18/01/2025

*Corresponding author: E-mail: darlingtonpeter2012@gmail.com;

Cite as: MARCEL-ONWUDIWE, Chinomnso Stella, Odidika Ugochukwu Joannes UMEORA, Joshua Adeniyi ADEBAYO, Darlington-Peter Chibuzor UGOJI, Ifeoma Cecilia UCHE-OMOVOH, Emmanuel Chijioke UWAKWE, Paschal Chijioke OKOYE, and Enemma Christian ENEMMA. 2025. "A Randomised Controlled Trial on the Effectiveness of Melatonin in Controlling Blood Loss During Ceaserean Section in a Tertiary Centre in Southeast Nigeria". *Asian Journal of Medicine and Health* 23 (1):69-77. <https://doi.org/10.9734/ajmah/2025/v23i11165>.

ABSTRACT

Background: Caesarean section is a common surgical procedure in Obstetrics. Despite the safety in carrying out caesarean section, it is still associated with blood loss and need for blood transfusion when compared to women who had vaginal delivery. Despite the use of uterotonic such as oxytocin, to prevent postpartum haemorrhage, excessive bleeding still occurs during and after caesarean section. Melatonin has been shown to reduce blood loss, which may be useful in prevention of postpartum haemorrhage. Hence, we aimed to determine the efficacy of Melatonin in reducing blood loss during and after elective caesarean section.

Methodology: This was a double-blind randomised controlled trial. Data analysis was done using IBM SPSS (version 25, Chicago II, USA). Continuous variables were presented as mean and standard deviation (Mean \pm 2SD), while categorical variables were presented as numbers and percentages. The categorical variables were analysed using Chi square, while means were compared using t-test and Mann-Whitney U test for non-parametric. A P value <0.05 was considered statistically significant.

Result: Sublingual melatonin reduced blood loss by an average of 76.67ml (0.44%) at elective caesarean section compared with placebo group (955.00ml versus 1031.67ml respectively), however this was not statistically significant (p-value = 0.097). Participants that received blood transfusion were higher in placebo group than melatonin group {29 (17.9%) versus 19 (11.7%)} however, the difference was not statistically significant (p-value = 0.159. Moreover, participants that required additional oxytocic were also higher in placebo group compared to melatonin group {45(27.8%) versus 34 (21.0%)} however, the difference between the two was not statistically significant, (p-value is 0.196). There was no major maternal or neonatal side effect.

Conclusion: This study demonstrated that 8mg sublingual melatonin did not significantly reduce blood loss at elective caesarean section. However, more participants in the placebo group required more oxytocic and blood transfusion. So higher doses and/or repetitive doses should be explored in future researches.

Keywords: Melatonin; blood loss; caesarean section; obstetrics; haemorrhage.

1. INTRODUCTION

Caesarean section is one of the most common surgical procedures in Obstetrics (Mamah et al., 2020; Bamigbala et al., 2022). Despite the safety in carrying out caesarean section, there increased risk of blood loss (Islam et al., 2022) and need for blood transfusion when compared to women who had vaginal delivery. The average blood loss during caesarean section is 498ml to 787ml (Khan et al., 2006). Postpartum haemorrhage (PPH) is a major cause of maternal morbidity and mortality worldwide (25%) with the highest incidence in developing countries (Sotunsa et al., 2019; Kalu and Chuhwurah, 2022). In Africa, it causes about 33.9% of maternal mortality and 23.0% in Abakaliki, Southeast Nigeria.

Administration of uterotonics, in particular oxytocin is the major component in preventing PPH due to uterine atony, but this can only prevent about 60% of postpartum haemorrhage (Obi et al., 2019) and a proportion of women will proceed to develop PPH despite this active management. Although oxytocin is the first-line

agent to prevent uterine atony during caesarean section, its use alone may sometimes, not be effective for prevention of PPH (Khezri et al., 2019). Apart from anaphylactic reactions, oxytocin, especially in high doses, has negative inotropic, antiplatelet and antidiuretic effects (Khezri et al., 2019). All these limits its use effectively.

Additional medications such as ergometrine, misoprostol and tranexamic acid have been investigated as the alternative and adjuvant therapeutic options for prevention and management of postpartum bleeding (Obi et al., 2019; Pakniat and Khezri, 2015). However, these drugs cannot be universally administered to patients as they are contraindicated in certain conditions. Melatonin (N-acetylmethoxytryptamine) plays a direct and integral role in uterine physiology in addition to its centrally mediated effects on reproduction (Khezri et al., 2019) and has been suggested as an adjuvant to oxytocin in prevention of postpartum haemorrhage (Khezri et al., 2019). It is cheap, easy to administer and readily available with minimal adverse effect, compared to other

drugs. In addition, it is stable at room temperature, thereby needs no refrigeration. Therefore, additional biochemical haemostatic effects obtained from the use of pro-haemostatic drugs such as melatonin may go a long way in complementing the effects of oxytocics in the prevention of PPH (Obi et al., 2019).

Melatonin levels increase in maternal blood, amniotic fluid and urine of pregnant women throughout pregnancy, reaching a peak at term (Tenorio et al., 2015). It is hypothesised that any change in the circulating melatonin level, which is synchronised with the light/dark cycle, is likely to be a major determinant of parturition time in pregnant women (Khezri et al., 2019). Olcese et al also reported that, melatonin acts through the MTNR1B melatonin receptor that is expressed in the myometrium at late term to synergistically enhance oxytocin-dependent signalling and contractions (Olcese and Beesley, 2014). Sublingual administration of melatonin (6mg) has been shown to reduce blood loss during caesarean section, although this was not clinically significant and further studies were recommended with higher dose of melatonin (Khezri et al., 2019). It is on this background we aimed to do this study.

2. METHODOLOGY

2.1 Study Design

This was a double blind randomised placebo controlled trial.

2.2 Study Population

The study was carried out among women undergoing elective caesarean section at Alex Ekwueme Federal University Teaching Hospital Abakaliki (AEFUTHA), and Mile four Hospital Abakaliki, Ebonyi state, Nigeria.

2.3 Study Duration

The study lasted for a period of seven months, between 19th May and 15th December 2022.

2.4 Inclusion Criteria

Pregnant women at low risk of postpartum haemorrhage at 37-42 weeks gestational age, on admission for elective caesarean section, who

gave consent to participate in the study and did not have any contraindication to the use of Melatonin were included in the study.

2.5 Exclusion Criteria

Women who have known allergy to Melatonin, prior history of thromboembolism, with bleeding disorders, history of renal disease, history of liver pathology, with varicose veins at increased risk of deep vein thrombosis, psychotic disorder, chronic anaemia, contraindication to regional anaesthesia, chronic hypertension/preeclampsia/eclampsia, antepartum haemorrhage, risk of primary postpartum haemorrhage such as multiple gestation, previous PPH, polyhydramnios, co-existing uterine masses

2.6 Sample Size Determination

The minimum sample size was determined using superiority formula for continuous variables (Zhong, 2009).

With it a Sample size of 81 was gotten. This was doubled to increase the power of the study to 162 per group.

3. RANDOMISATION AND CONCEALMENT

The participants were recruited by simple randomization. The participants were randomised by means of a computer generated random numbers using the software Research Randomizer. Using this software, one hundred and sixty-two numbers were randomly generated from a pool of three hundred and twenty-four numbers (1-324). These were assigned to group A (Melatonin group) while the remaining 162 random numbers were assigned to group B (the placebo group). These numbers were inscribed on a piece of paper with the corresponding group written along with the numbers. These numbers (1-324) were also written on brown envelopes and the pieces of paper inserted into the corresponding envelopes. They were then arranged sequentially from 1 to 324.

Concealment of the drugs was done in the sequentially-numbered opaque sealed envelopes (SNOSE) by a hospital pharmacist without revealing the code to the researcher. All the envelopes were kept in a locker that was made accessible to all the members of the research team.

Participants who meet the inclusion criteria, having signed the informed consent form was given sequential study number and the corresponding numbered opaque sealed envelope was then allocated to the patient.

Group A: Received 8mg of sublingual melatonin during preloading, approximately 20 minutes before spinal anaesthesia. (That is, two tablets of melatonin 5mg and 3mg).

Group B: Received 200mg of sublingual vitamin C during preloading approximately 20 minutes before spinal anaesthesia. (That is, two tablets of 100mg of vitamin C).

3.1 Blood Loss Estimation

a. Haematocrit value: The estimated blood loss was measured using the difference in haematocrit values taken before the surgery and 48 hours after the caesarean section using the formula below.

$$EBL = \text{Pre-operative Haematocrit} - \text{Post-operative haematocrit}$$

Where EBL= Estimated blood loss

Blood loss greater than >1000ml was regarded as excessive bleeding.

b. Visual estimation of blood loss: Blood loss was also estimated by visual method. This is the commonest method of estimating blood loss by obstetricians and anaesthetists. As swab count is a universal method for estimating blood loss at caesarean section, Bose P. and colleagues developed a standardized measure of visual estimation of blood loss using swab count and floor spill (Bose et al., 2006).

3.2 Follow Up

The participants were monitored during their stay in the hospital. They were seen 4 hours after caesarean section to check for postpartum

haemorrhage and any other problem. They were also seen on day one, two and day 3. They were followed up until discharge from the facility. The participants were discharge after 4 to 5 days unless there is reason for longer hospital stay. They were instructed to present to the hospital or reach the researcher or any of the research assistants by phone if they have any unforeseen adverse reaction. And they were seen at the postnatal clinic by the managing team at six weeks postpartum.

3.3 Outcome Measures

Primary Outcome Measure is; quantity of blood loss during caesarean section.

Secondary Outcome Measures are

1. The need for additional uterotonics to control bleeding.
2. The need for blood transfusion during or after the surgery
3. Maternal side effects (nausea, vomiting, headache, skin rash, dizziness, hypotension, bradycardia and maternal death)
4. Neonatal side effect.

3.4 Statistical Analysis

Data was collated, tabulated then statistically analysed using IBM SPSS software (version 25, Chicago II, USA). Continuous variables were presented as mean and standard deviation (Mean \pm 2SD), while categorical variables were presented as numbers and percentages. Chi-square test (X^2) was used for comparison between groups for categorical variables while student t-test and Man-Whitney U test was used for comparison between groups for continuous variables. A difference with a p-value <0.05 was considered statistically significant.

Table 1. Guidelines for visual estimation of blood loss (Bose et al., 2006)

| | |
|--|---------|
| Small, 10-x10-cm 32 ply swab (maximum saturated capacity) | 60 ml |
| Medium, 30- x 30-cm 12 ply swab (maximum saturated capacity) | 140 ml |
| Large, 45- x 45-cm 12 ply swab (maximum saturated capacity) | 350 ml |
| 1-kg soaked swabs | 1000 ml |
| 50-cm diameter floor spill | 500 ml |
| 75-cm diameter floor spill | 1000 ml |
| 100-cm diameter floor spill | 1500 ml |
| Vaginal PPH limited to bed only Unlikely to exceed | 1000 ml |
| Vaginal PPH spilling over from bed to floor Likely to exceed | 1000 ml |

4. RESULTS

Over the study duration of seven months, 356 patients were assessed for randomisation into the study. Thirty-two were excluded while 324 were allocated to receive either the melatonin or placebo.

4.1 Consort Diagram

Table 2 showed no statistically significant difference in all the socio-demographic variables between the two groups.

Table 3 showed no statistical significant difference in the mean duration of surgery in both groups. Also there was no significant difference in neonatal weight and the APGAR scores in the first and fifth minute, (p-value >0.05).

The estimated blood loss by visual estimation was lower in the melatonin group than placebo

group (479.01±111.28ml versus 481.17±109.06ml). The difference between the two was not statistically significant (p = 0.860). More so, blood loss using haematocrit was lower in the melatonin group compared to the placebo group (955.00ml versus 1031.67ml respectively) (p-value 0.097). In other words, melatonin reduced blood loss by 76.67ml (0.44%). There was no significant difference in the pre-operative haematocrit values between both groups p-value was 0.248. But the mean post-operative haematocrit was significantly higher in the melatonin group compare with the placebo group with p-value of 0.019. The change in haematocrit was also higher in placebo group compare to melatonin, but the difference was not statistically significant (p = 0.058).

Table 4 showed that the difference indications for caesarean section between the two groups were not statistically significant p-value >0.05

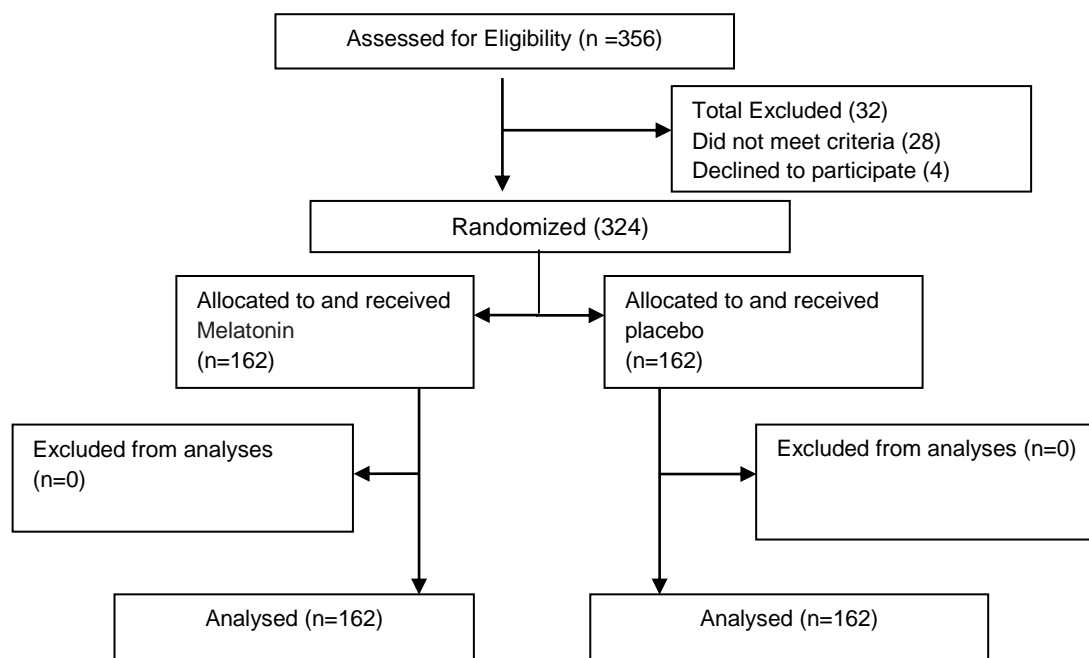


Fig. 1. the flow of patients through the study

Table 2. Demographic characteristics of the patients and some surgery determinants

| Variables | Melantonin (n=162) | Placebo (n=162) | t-test | P-value |
|--------------------------------------|--------------------|-----------------|-----------|---------|
| Maternal age (years) | 30.79±5.90 | 29.54±6.23 | 1.851 | 0.065 |
| Height (m) | 1.59±0.06 | 1.60±0.07 | 1.377 | 0.168 |
| Weight (kg) | 78.14±12.54 | 80.01±13.97 | 1.866 | 0.206 |
| Body Mass Index (kg/m ²) | 30.54±4.68 | 31.04±5.35 | 0.896 | 0.371 |
| Gestational age (weeks) | 39.10±1.77 | 38.81±2.35 | 1.254 | 0.211 |
| Parity (median, range) | 1 (0-6) | 1 (0-6) | 11929.00* | 0.146 |

*Mann-Whitney U test used for non-parametric

Table 3. Surgical determinants

| Variables | Melantonin (n=162) | Placebo (n=162) | t-test | P-value |
|---------------------------------|-----------------------|--------------------|--------|---------|
| Mean duration of surgery (mins) | 60.57±12.06 | 60.37±13.19 | 0.144 | 0.887 |
| Fetal birth weight (kg) | 3.04±0.58 | 3.14±0.65 | 1.418 | 0.157 |
| APGAR Scores | | | | |
| First minute | 9.47±0.77 | 9.38±0.70 | 1.099 | 0.272 |
| Fifth minute | 9.98±0.16 | 9.94±0.24 | 1.641 | 0.102 |

Table 4. Indications for the surgery

| Variables | Melantonin (n=162) | Placebo (n=162) | χ ² | P-value |
|---|-----------------------|--------------------|----------------|---------|
| Two previous scars | 26(44.8%) | 32(55.2%) | 0.763 | 0.385 |
| ≥3 previous scars | 18(62.1%) | 11(37.9%) | 1.859 | 0.173 |
| One previous scar with another indication | 28(56.0%) | 22(44.0%) | 0.854 | 0.356 |
| Breech presentation | 20(54.1%) | 17(45.9%) | 0.266 | 0.600 |
| Transverse lie at term | 7 (53.8%) | 6 (46.2%) | 0.081 | 0.777 |
| Fetal Macrosomia | 27(56.2%) | 21(43.8%) | 0.881 | 0.348 |
| Intrauterine growth restriction | 10(16.7%) | 20(83.3%) | 3.673 | 0.055 |
| Others | 26(44.1%) | 33(55.9%) | 1.024 | 0.314 |

Table 5a. Intraoperative and postoperative variables

| Variables | Melantonin (n=162) | Placebo (n=162) | t-test | P-value |
|-----------------------------|-----------------------|--------------------|--------|---------|
| EBL (in ml) | 479.01±111.28 | 481.17±109.06 | 0.176 | 0.860 |
| EBL (in %) | 5.73±2.47 | 6.19±2.50 | 1.673 | 0.097 |
| Maternal haematocrit | | | | |
| Preoperative | 32.81±2.79 | 33.25±3.90 | 1.157 | 0.248 |
| Post-operative | 27.95±2.21 | 27.32±2.58 | 2.361 | 0.019 |
| Change in haematocrit | 4.99±2.53 | 5.61±3.28 | 1.914 | 0.058 |

Table 5b. Intraoperative and postoperative variables and maternal outcomes in the study group and in the placebo group

| Variables | Melatonin (n=162) | Placebo (n=162) | P-value | Odd Ratio (95% C.I. OR) |
|----------------------------|----------------------|--------------------|---------|----------------------------|
| Blood loss (ml) | | | | |
| ≥1000 | 48 (29.6%) | 61(37.7%) | 0.158 | 0.70 (0.44-1.11) |
| <1000 | 114(70.4%) | 101(62.3%) | | |
| Additional oxytocic | | | | |
| Yes | 34 (21.0%) | 45 (27.8%) | 0.196 | 0.69 (0.41-1.15) |
| No | 128(79.0%) | 117(72.2%) | | |
| Blood transfusion | | | | |
| Yes | 19 (11.7%) | 29(17.9%) | 0.159 | 0.61 (0.33-1.14) |
| No | 143(88.3%) | 133(82.1%) | | |
| Side effects | | | | |
| Headache | 33(20.4%) | 42(25.9%) | 0.292 | 0.73 (0.43-1.23) |
| Vomiting | 8 (4.9%) | 16 (9.9%) | 0.136 | 0.47 (0.20-1.14) |
| Nausea | 4 (2.5%) | 5 (3.1%) | 1.000 | 1.34 (0.30-6.09) |
| PPH | | | | |
| Yes | 48 (29.6%) | 61(37.7%) | 0.126 | 2.344* |
| No | 114(70.4%) | 101(62.3%) | | |

*Chi-square test used, PPH – Primary postpartum haemorrhage

Table 6. Fetal outcome

| Variables | Melantonin | | Placebo | | t-test | P-value |
|----------------------------|------------|-----------|---------|-----------|--------|---------|
| | N | Mean ±SD | n | Mean ±SD | | |
| APGAR Score at 1min | | | | | | |
| APGAR 7-10 | 162 | 9.47±0.77 | 162 | 9.38±0.70 | 1.099 | 0.272 |
| APGAR Score at 5min | | | | | | |
| APGAR ≥ 9 | 162 | 9.98±0.16 | 162 | 9.94±0.24 | 1.641 | 0.102 |

Table 6 was not statistically significant.

Table 5b showed that blood loss ≥ 1000 ml was lower in melatonin group compared to placebo group. The difference between the two was not statistically significant giving the Odd ratio = 0.70, 95% confidence interval = 0.44-0.11 and p-value 0.158. The participants that required additional oxytocic's were higher in placebo group compare to melatonin group but the difference is not statistically significant (p-value 0.196). Participants who received blood transfusion were also higher in placebo group than melatonin group but also not statistically significant (p-value 0.159). Difference between the participants that had headache, vomiting and nausea in both groups were not statistically significant (p-values > 0.05). There were no other side effects observed in the participants. There was no maternal mortality.

5. DISCUSSION

This study showed that, pre-operative administration of 8mg of sublingual melatonin reduced blood loss during caesarean section by 76.67ml (0.44%). This might be due to the fact that, melatonin augments oxytocin activity and enhances myometrial cell contractions leading to reduce blood loss (Sharkey et al., 2010 ; Sharkey et al., 2009). The second possible reason is that, melatonin prevents high blood pressure and excessive haemorrhage by reducing anxiety (Khezri et al., 2019). This finding was higher than 68.33mls (0.41%) by Khezri et al (2019) and 55ml (0.33%) by Javadi et al (2021). This difference may be due to the difference in sample size and dosage of melatonin. While Khezri et al and Javadi et al had smaller sample sizes (40 and 70 respectively) the sample size of the current study was 162 per group. Also, Javadi et al study was among pregnant women that delivered vaginally while ours was among women that delivered by elective caesarean section. Also, their haemoglobin estimation was done 24 hours postpartum while our postpartum haematocrit was done after 48 hours. Moreover, Khezri et al use lesser dosage of melatonin, 6mg

while 8mg of melatonin was used in our study. Khezri et al did their postoperative haemoglobin after 12 hours while ours was done 48 hours post-operative.

The mean blood loss in melatonin group was 955.00ml, while the mean blood loss in placebo group was 1031.67ml. The difference between the two was not statistically significant with p-value of 0.097. This might be due to dosage of melatonin used. This finding was similar to that found by Khezri et al (2019) and Jayeshree et al (2021). This similarity might be due to low dosage of melatonin, Khezri and Jayeshree et al used 3mg and 6mg of melatonin respectively and we used 8mg. The difference between 6mg and 8mg is not much. May be a higher dose of melatonin is needed. However, Khezri et al had found a significant blood in 6mg of melatonin that may not be clinically meaningful (Khezri et al., 2019) did study with 3mg and 6mg of melatonin). This difference may be due to difference in sample size. Khezri et al used 40 participants per group while we used 162 participants per group. In addition, Khezri et al did postpartum haemoglobin after 12 hours, haemodilution may have not taken place. Our findings also differ from Javadi et al (Javadi et al., 2021). Javadi et al found that melatonin can significantly reduce blood loss during vaginal delivery. The difference may be due to the difference in dose of melatonin Javadi et al used 12mg of melatonin while we used 8mg. Also Javadi et al did their study among women that underwent vaginal delivery while our participants underwent elective caesarean section.

Furthermore, this study also demonstrated that pre-operation sublingual melatonin reduced the need for additional uterotonics during caesarean section compared to placebo which was not statistically significant. The possible explanation for this finding could be the gradual effect of melatonin which may not be clinically apparent. This finding was similar to that by Khezri et al (2019) where there was insignificant difference in the dose of oxytocin used between the groups. This similarity may be due to the dosage of

melatonin used by Khezri (6mg) and the dosage of melatonin used in this study. The difference is not much, 6mg and 8mg respectively.

In addition, this study demonstrated that melatonin reduced incidence of primary postpartum haemorrhage. This finding is similar to that of Jayashree et al (Jayashree et al., 2021). The similarity might be due to similar dosage regimen, 6mg and 8mg. Also it might be due to the fact that our participants and theirs underwent caesarean section.

Also, this study showed that there was increase in blood transfusion among the participants who received placebo more than those that received melatonin. This might be due to the fact that, melatonin augments oxytocin activity and enhances myometrial cell contractions leading to reduce blood loss (Sharkey et al., 2010; Sharkey et al., 2009). The second possible reason is that, melatonin prevents high blood pressure and excessive haemorrhage by reducing anxiety (Khezri et al., 2019). The previous studies did not record their blood transfusion. Javadi et al excluded those that had blood transfusion and additional uterotonics (Javadi et al., 2021).

Only minor side effects such as nausea, vomiting and headache were observed among the participants in this study. The difference between the two groups was not statistically significant. This may be due to the fact that we did not use very high dose of melatonin. This demonstrated that melatonin is safe and have no adverse maternal outcome. These findings were similar to that of Jayashree et al (Jayashree et al., 2021), this may be due to similarity in the dosage of melatonin, Jayashree used 6mg while we used 8mg. Both are not very high dose of melatonin. This findings differ from that found by Khezri et al (2019). Khezri et al recorded that, the incidence of headache in 6mg melatonin group was significantly higher in melatonin group than placebo group. This difference may be due to the difference in sample size. Khezri et al use 40 participants per group while we used 162 participants per group.

Moreover, this study also noted that, there was no difference in the neonatal APGAR scores in first and fifth minute between the two groups and there was no new-born intensive care unit admission and no perinatal death. This might be due to the fact that we did not use very high dosage of melatonin and only those booked for elective caesarean section were recruited. This finding is similar to that found by Khezri et al (2019). This might be because, we and Khezri

used a similar dosage of melatonin (8mg, and 6mg respectively). Also participants that were booked for elective caesarean section were recruited in our study as well as by Khezri et al. In addition, Javadi et al (2021) also recorded a similar finding. This further suggests that melatonin did not have any adverse maternal or neonatal outcome.

6. CONCLUSION

This study demonstrated that 8mg sublingual melatonin did not significantly reduce blood loss at elective caesarean section. However, more participants in the placebo group required more oxytocin's and blood transfusion.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

ETHICAL Approval

Ethical clearance was sought and obtained from the Health Research and Ethics committee of the Alex Ekwueme Federal University Teaching Hospital, Mile 4 Hospital Abakaliki and National Obstetrics Fistula Centre Abakaliki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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