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Effect of melatonin in reducing blood loss during and after caesarean section

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Abstract
Background and Objectives: Obstetric blood loss is one of the feared complications of child birth. Blood loss during caesarean section is twice than that of vaginal delivery. The aim of this study is to evaluate the effect of preoperative single sublingual dose of melatonin in reducing blood loss after caesarean section when comparing with placebo.
Methods: The subjects of this prospective randomised placebo controlled study were 60 pregnant women who were admitted in the labour ward, in the time period from May 2019 to April 2022. Thirty patients were placed in group A as cases and thirty patients were placed in group B as control. All patients were counselled and informed consent obtained. Group A received 6 mg of sublingual Melatonin 20 minutes before skin incision and Group B received sublingual use of placebo 20 minutes before skin incision.
Results: No significant difference of blood loss from incision to end of CS (328 ml vs 321 ml) - p value 0.358. Blood loss reduced from end of CS to 2 hrs PP (55 ml to 53ml) but not statistically significant. P value – 0.696
Conclusion: Melatonin, when given prophylactically 20 minutes before skin incision by sublingual route in caesarean section appears to reduce the blood loss which is statistically in significant.

Keywords: proximal tibia fracture, MIPPO, knee stiffness, wound dehiscence

Introduction

Caesarean section is one of the commonest operative procedure done in the world. Incidence of caesarean section is increasing throughout the world because of social factors like advanced maternal age, improved surgical techniques and increasing litigation problems.

Although caesarean section delivery is much safer today due to improved techniques but still it is a major cause of intraoperative and post-operative complications with higher morbidity and mortality than with vaginal delivery.

Although caesarean delivery is more traumatic than an easy vaginal delivery but an elective caesarean section is preferred over a difficult vaginal delivery to reduce maternal and neonatal morbidity and mortality.

Obstetric blood loss is one of the feared complications of child birth. Blood loss during caesarean section is twice than that of vaginal delivery.

The rate of caesarean section has increased by 10 to 20% in the past ten years worldwide. Caesarean section, compared to normal vaginal delivery has significant complications and blood loss which thereby increases maternal morbidity and mortality [1].

Post-partum haemorrhage is one of the leading cause of death in maternal mortality [2]. Therefore, to reduce maternal morbidity and mortality it is important to reduce the blood loss during and after lower segment caesarean section [3].

The similarities between the melatonin and oxytocin signaling could lead to increased contractility of myometrium.

MEL was found to synergistically enhance OT-induced contractility via the MT2R, which is coupled to a protein kinase C-dependent increase in phosphorylation of the myosin light chain protein. MT2R expression was markedly elevated in samples from pregnant women who had entered labour, as compared to matched nonlaboring pregnant women. MEL increased expression of the gap junction protein, connexin 43. *In vitro* dye spread assays showed that MEL-treated cells displayed substantially increased intercellular coupling. Increase in Connexin 43 mRNA and cell to cell coupling were also found to be mediated via the MT2R in a protein kinase C-dependent manner.

MEL synergizes with OT to promote myometrial cell contractions and to facilitate gap junction activity *in vitro*. Such a synergy *in vivo* would promote coordinated and forceful contractions of the late term pregnant uterus necessary for parturition.

Incidence

Caesarean section is one of the commonest operative procedure done in the world. Its incidence has been quadrupled between 1965-1988 because of various factors. Current rate of caesarean section in most of the countries is between 25-40%. But WHO says that there may be no health benefits from caesarean section rates exceeding 15%.

A mandatory second opinion was associated with a small but significant reduction in caesarean rate without an adverse effect on maternal or perinatal morbidity. (Althabe *et al*. 2004).

Maternal morbidity dramatically increases with caesarean section when compared with vaginal delivery. (Burrows *et al* 2004) and the cost of caesarean section two fold increases than that of vaginal delivery. (Henderson *et al*. 2001). So risks and benefits need to be weighed.

Blood loss during Caesarean Section

Normal blood loss during vaginal delivery may be up to 500 ml, but a lower value of 300ml should be considered for Asian countries as they may be unable to cope up with a large amount of blood loss due to their small build and lower antenatal Hb. (Ratnam and Rauf *et al*. 1989)

Blood loss during caesarean section is twice than that of vaginal delivery that is up to 1000 ml (Driffe 1997).

Post-partum haemorrhage is defined as,

1. Blood loss of more than 500 ml following vaginal delivery, more than 1000 ml following caesarean delivery and more than 1500 ml after caesarean hysterectomy.
2. Any post-partum bloodloss which needs blood transfusion or causes fall in haematocrit by 10% (ACOG-definition).
3. Any postpartum blood loss causing haemodynamic instability or if untreated leads to haemodynamic instability.

Incidence of PPH

The incidence is 2 to 11% when blood loss is estimated visually (Brant *et al* 1967) and 20% when blood loss is estimated by quantitative methods (Newton *et al* 1961).

Blood loss estimated by visual observation method will always be less than that of actual bloodloss (Pritchard 1962).

Materials and Methods

Participant and study design

The main source of data for this study are patients from Rajah Muthiah Medical College and Hospital, Annamalai University. The subjects of this prospective randomised placebo controlled study were 60 pregnant women who were admitted in the labour ward, in the time period from May 2019 to April 2022.

In all patients detailed history – medical history, obstetric history were taken. Vital parameters checked and basic investigations done. Weight of the patient was checked. Detailed general examination and obstetric examination was done. Gestational age was confirmed by Ultra sound examination.

30 patients were placed in group A and 30 patients were placed in group B. All patients were counselled and informed consent obtained.

Group A CASES received

1. 6 mg of sublingual Melatonin – 20 minutes before skin incision.
2. Oxytocin 10 units in IV infusion immediately after the delivery of the baby.

Group B controls received

1. Sublingual use of placebo 20 minutes before skin incision.
2. Oxytocin 10 units in IV infusion immediately after the delivery of the baby.

Methods

Group A and Group B patients received the drugs as mentioned above. In each case the following parameters were checked and documented.

1. Preoperative PR / BP / RR / Hb%
2. Intraoperative blood loss from placental delivery to end of surgery. The study ignored the amniotic fluid and bleeding occurred prior to placental delivery.
3. Post operative blood loss from the end of surgery to 2 hours post partum.
4. Post operative PR, BP, RR, Hb%
5. Side effects of the drug
6. Maternal needs for blood transfusion.
7. Post operative period and the maternal outcome till discharge.
8. Neonatal outcome.

Measurement of Blood loss

In this study blood loss was measured by measuring the blood in the suction container after placental delivery and by weighing the swabs before and after surgery.

1 gm of swab weight = 1 ml of blood
(Bonica and Lyter 1951 / Harding 1984)

$$\text{Total blood loss (ml)} = \left[\begin{array}{c} \text{Swab weight} \\ \text{after surgery (gm)} \end{array} - \begin{array}{c} \text{Swab weight} \\ \text{before surgery (gm)} \end{array} \right] + \text{Blood in the suction container (ml)}$$

Intraoperative Blood loss will be assessed from

1. Gauze count, Pad count
2. Amount of blood collected in suction apparatus
3. Fall in BP and rise in heart rate
4. Urine output
5. Weight of the dry pad / wet pad

Post-operative blood loss

1. Haematocrit
2. Haemoglobin

Even-though this gives only the approximate amount of blood loss it is the only practically possible and feasible method. Hence these methods were used in this study.

After collecting, the data was tabulated in a master chart and analysed. Data analysis was done with the help of computer using Epidemiological information package (2008).

Using this software frequencies, percentage, mean, Standard Deviation, chi-square and 'p' values were calculated. Kruskul Wallis chi square test was used to test the significance of difference between quantitative variables and Yate's test for

qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

Results

This study was conducted in the Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital, Chidambaram from May 2019 to April 2022, to evaluate the effect of preoperative single sublingual dose of melatonin in reducing blood loss after Caesarean section. It was clinically observed that the blood loss was reduced by sublingual use of 6mg of melatonin during and after caesarean section.

The possible confounding factors like age, height, weight & gravidity were comparable in both the groups.

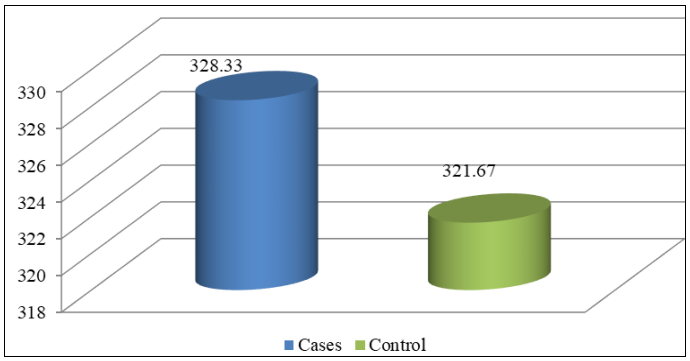
Distribution with respect to indication of LSCS like fetal distress, cephalopelvic disproportion, abnormal presentation, previous LSCS & arrest of descent was comparable in both the groups.

- 60 patients were selected for the study, 30 as case group and 30 as Control group.
- No significant difference (p=0.275) between mean age of the patients of both control and study group.
- Mean weight of the patients of both groups are not significant. (p=0.104)
- No significant difference (p=0.633) between mean gestational age of the patients of both control and study group.
- No significant difference of blood loss from incision to end of CS (328 ml vs 321 ml) - p value 0.358.
- Blood loss reduced from end of CS to 2 hrs PP (55 ml to 53ml) but not statistically significant. p value 0.696.
- No significant difference between Systolic and Diastolic Bp and Pulse rate between both groups.
- Only 2 cases had nausea, but had no statistical difference regarding complications of both groups.

Table 1: Blood Loss

Blood Loss from Incision to end of CS in ml	Cases	Control
< 300	5	11
> 300	25	19
Total	30	30
Mean	328.33	321.67
SD	21.35	33.12
'P' value	0.358 Not significant	

No significant difference in blood loss from incision to end of CS. P value 0.358 was not significant.

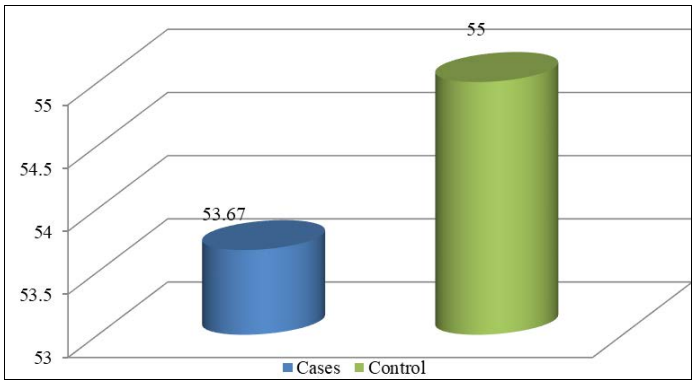


Graph 1: Comparison of blood loss from incision to end of CS

Table 2: Blood Loss from end of CS to 2 HRS PP

Blood Loss from CS to 2hrs PP in ml	Cases	Control
< 50	17	16
> 50	13	14
Total	30	30
Mean	53.667	55
SD	12.452	13.834
'P' value	0.696 Not significant	

No significant difference in blood loss from CS to 2 hrs PP. P value 0.696 was not significant.

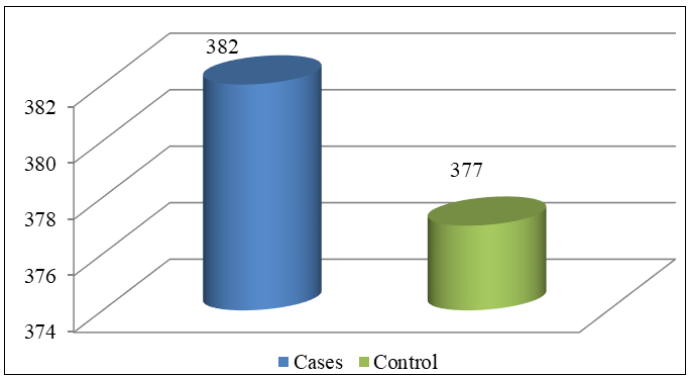


Graph 2: Blood loss from end of CS to 2 hours PP

Table 3: Comparison of Total Blood Loss

Total Blood Loss in ml	Cases	Control
< 350	5	8
> 350	25	22
Total	30	30
Mean	382	377
SD	26.182	36.403
'P' value	0.544 Not significant	

No significant total blood loss between cases and control. P value 0.544 was not significant.



Graph 3: Comparison of total blood loss

Table 4: Comparison of Hb

Hb in g% before delivery		
	Cases	Control
< 11	16	18
> 11	14	12
Total	30	30
Mean	11.02	10.947
SD	0.747	0.564
'P' value	0.669 Not significant	

Hb in g% after delivery		
	Cases	**Control**
< 10	11	6
> 10	19	24
Total	30	30
Mean	10.443	10.53
SD	0.766	0.611
'P' value	0.63 Not significant	

No significant difference was found between cases and control regarding Hb level before and after delivery.

Discussion

As obstetric blood loss contributes to one fourth of global maternal death its incidence has to be reduced.

As prevention is always better than cure regarding PPH - sublingual use of 6mg of melatonin was used prophylactically in this study to observe its efficacy in reducing blood loss during and after caesarean section.

Our study showed that Melotonin reduces bleeding from the time of placental delivery to 2 hrs postpartum in LSCS. Results show that study group patients had mean blood loss of 53.6ml ± 12.5 as standard deviation, while control group patients had mean blood loss of 55ml ± 13.4 as standard deviation. There was reduction in blood loss in both the parameters, i.e. from time of placental delivery to completion of skin closure & from completion of skin closure to 2 hrs postpartum. Melotonin also reduced the incidence of postpartum haemorrhage in the study group as compared to control group. In this study nil cases were noted in study group and 4 cases in control group and P-0.085 is insignificant. But other studies have shown significant decrease in PPH in patients who received Melotonin.

The side effects of Melotonin as nausea, vomiting & diarrhea were not statistically significant in both the groups in this study. These results were similar with previous studies.

Oxytocin on high doses has Antiplatelet, Inotrophic and antidiuretic action, it's action alone is not sufficient to control PPH, so need some additional drugs like Misoprostol and ergot alkaloids in compromised patients [1, 2, 3], Tamura and Nakamura study [4] concluded that presence of MT1 and MT2 receptors in uterine myometrium enhances uterine contractility. In Tenorio FD study [5], maximum Melatonin levels will be present in Maternal blood, Amniotic fluid, Urine of pregnant mother, Melatonin also had some beneficial effect on Placenta and fetus [6, 7] Similarities between Oxytocin and Melatonin signaling increased uterine myometrial contraction [8, 9, 10].

Melatonin has anxiolytic action and prevents high Blood pressure due to pain anxiety and fear and reduces haemorrhage during labour [11, 12, 13, 15], Endogenous Melatonin, enhances nocturnal uterine activity which is suppressed by light [14], so it plays a role in timing of delivery, Melatonin has sedation effect if its given 20mins before delivery [16], It is used to relieve Migraine and cluster headache by inhibiting nitric oxide activity, dopamine release and free radical scavenging mechanisms [17, 18]. It reduces the intracranial tension and brain edema [20, 21] in traumatic brain injury patients.

Conclusion

Sublingual use of 6mg of melatonin 20 minutes before surgery as a premedication reduces blood loss in caesarean section without any serious complications which is statistically insignificant. So further studies may be needed to study the efficacy of this drug.

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