Melatonin as an adjuvant for induction of labour (IOL): a double-blind, randomised, placebo-controlled trial (MILO Trial)

Melatonin may help primiparous women undergoing IOL with balloon catheter

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INTRODUCTION

Melatonin has been shown to have important physiologic effects in spontaneous labour.[1-5] Our team investigated whether adding melatonin to oxytocin in induction of labour (IOL) could help reduce caesarean section (CS) rates for women.

METHODS

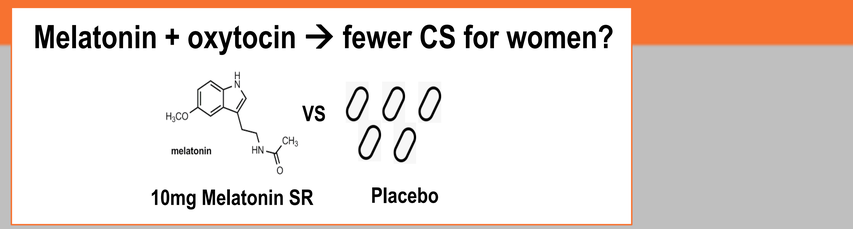
Population:
Low-risk women between 18-50 years of age, of Para 0-3 having IOL at term with a live cephalic baby, free from any medical or obstetric complications and who were not taking any medications that can interact with melatonin pharmacokinetics were invited to participate in our trial.

Intervention / **C**omparison:
Women were randomized to placebo tablets or 10mg slow release (SR) melatonin tablets

- Please refer to Figure 1 for trial protocol
- If requiring ripening women received an extra dose the night before IOL with insertion of cervical ripening device (CRD)
- Otherwise women took trial tablets 6hrly to a maximum of 4 doses or until birth on their IOL day with commencement of oxytocin infusion
- Bloods were taken at baseline, 3h post initial dose and birth to determine circulating melatonin levels

Outcome

- The primary outcome was caesarean section rate
- Secondary outcomes included a combination of maternal and neonatal safety measures



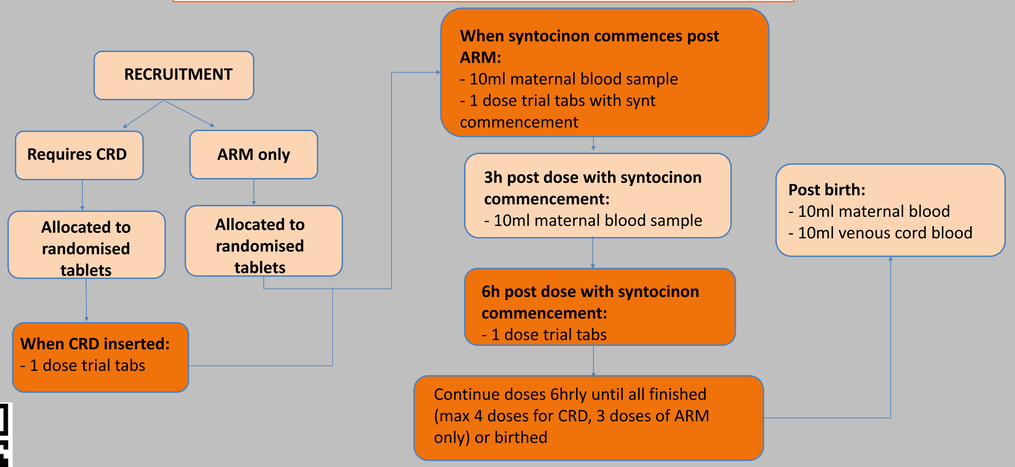


Figure 1 – trial protocol

View full abstract & References

RESULTS

187 women were recruited to the trial – **103** in the melatonin arm and **84** in the placebo arm

- Both groups had comparable baseline characteristics

Primary outcome – caesarean section rates

- Melatonin overall not shown to reduce CS rates (RR 1.1; 95% CS 0.67-1.82)

PRIMARY OUTCOME – CS RATES	Melatonin (n=103)	Placebo (n=84)
Caesarean Birth	27(26.2%)	20(23.8%)
+within 24 hours of IOL	7(6.79%)	5(5.95%)
Caesarean birth for failure to progress	10(9.7%)	5(6%)
Caesarean birth for suspected fetal distress	10(9.7%)	9(10.7%)

Secondary outcomes

Maternal

- Nil significant difference in length of labour, uterine hyperstimulation, total dose of oxytocin use, rates of PPH or maternal admission to HDU/ICU
- Similar rates of maternal satisfaction between both groups
- 18% of melatonin group reported side effects vs 9.5% in placebo group (most commonly sleepiness & gastrointestinal upset)

MATERNAL SECONDARY OUTCOMES	Melatonin (n=103)	Placebo (n=84)	P value
Length of labour (mean mins) (min-max)	314 (142-537)	269 (110-507)	0.55
Uterine hyperstimulation	14(22.5%)	15(25.9%)	0.68
Total oxytocin dose (mean units) (min-max)	3.9 (1.08-9.26)	3.52 (0.89-10.31)	0.94
Postpartum Haemorrhage	31(30.1%)	23(27.4%)	0.68
Maternal HDU/ICU admission	0(0%)	1(1.2%)	0.27

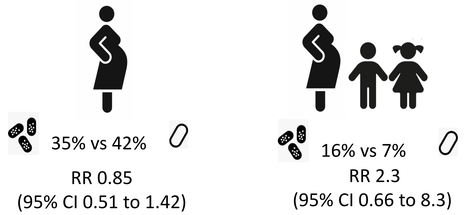
Neonatal

- nil significant difference in rate of 5min Apgar score <7, admission or cord lactates.
- **Neonates born to the melatonin arm were more likely to be admitted to Special Care Nursery for BSL monitoring**
- 5.8% of babies in melatonin arm also reported to be sleep compared to 1.2% in placebo group – but nil issues reported with regards to feeding or respiratory compromise

NEONATAL SECONDARY OUTCOMES	Melatonin n=103	Placebo (n=84)	P value
Apgar score <7 at 5 min	24(23.3%)	15(17.9%)	0.36
Admission to Neonatal Intensive Care Unit	3 (2.91%)	3 (3.57%)	0.80
Admission to Special Care Nursery	19 (18.45%)	7 (8.33%)	0.047
Arterial Umbilical Lactates*	5.05(2.0)	5.07(1.71)	0.97
Venous Umbilical Lactates#	3.7(1.8)	3.7(1.4)	0.91

Sub-group analyses – primiparous vs multiparous women

- **Primiparous** women receiving melatonin were **less likely** to need CS as compared to placebo; however **multiparous** women were **more likely** to require CS if taking melatonin compared to placebo



Sub-group analyses – mode of ripening agent

- Women receiving balloon catheter ripening and melatonin were less likely to need CS compared to women receiving prostaglandin ripening or nil ripening in the melatonin arm

CS RATE BASED ON RIPENING AGENT	Melatonin n=103	Placebo (n=84)	RR (95% CI)
Foley catheter	27%	39%	0.7 (0.4-1.22)
Prostaglandin	15%	7%	2.2 (0.4-11.2)
Nil ripening (ARM only)	43%	15%	2.8 (0.7-11.4)

CONCLUSIONS

Melatonin overall was not shown to reduce CS rates but there is a potential benefit in the subgroup of primiparous women undergoing IOL via balloon ripening.