ORIGINAL ARTICLE

Is lower dose of intramuscular dexamethasone injection beneficial in reducing neonatal respiratory morbidity for elective caesarean section deliveries at 37 to 38 weeks? An observational study

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ABSTRACT

Introduction: The use of intramuscular (IM) dexamethasone injections before an elective caesarean delivery at term has been shown in multiple randomized controlled trials to reduce the rates of transient tachypnoea of the newborn, and admission to neonatal care. Recent studies have suggested that a complete course of IM steroids can be associated with long term harmful consequences to the infants born, and there have been studies suggesting that a lower dose of IM corticosteroids can be beneficial. Therefore, we aim to establish if halving the dose of dexamethasone to 12mg can demonstrate any benefit for term elective caesarean section deliveries whilst minimizing foetal exposure.

Methods: An observational controlled study comparing neonatal respiratory morbidities before and after the single dose 12mg dexamethasone was implemented in our obstetrics and gynaecology centre for term elective caesarean section deliveries.

We included singleton pregnancies from 37+0 to 38+6 weeks undergoing elective caesarean section into our study. A total of 674 patients fulfilled the inclusion criteria and were recruited. We compared the rates and duration of admission to neonatal intensive care unit, the need for mechanical ventilation and the rate of transient tachypnoea of the newborn in the first half of 2019 without IM dexamethasone injections against the second half of the year when a single dose IM dexamethasone was given.

Results: IM dexamethasone injection did not show any significant benefit with regards to reducing the admission to neonatal care (OR 0.97, p- value 0.69), admission to neonatal intensive care unit (OR 0.91, p- value 0.80), the need for mechanical ventilation (OR 0.98, p- value 0.95), and the incidence of transient tachypnoea of the newborn (OR1.01, p- value 0.96). There was also no significant difference for the duration of admission in the neonatal intensive care unit for both groups (p- value 0.17).

Conclusions: This study showed that there was no significant benefit gained from the lower dose antenatal corticosteroids for term elective caesarean section deliveries and considering that there have been long term harmful consequences demonstrated from the higher dose of antenatal corticosteroids at term, this practice should therefore be discontinued until a larger study is done to refute these findings. The use of such dexamethasone should only be a viable option in a research setting.

KEYWORDS:
Antenatal corticosteroids, dexamethasone, transient tachypnoea of the newborn, respiratory distress syndrome

INTRODUCTION

In 1972, it was first demonstrated by Liggins and Howie that the administration of corticosteroids to preterm pregnancies prior to delivery reduces the morbidity and mortality of preterm infants. These revolutionary findings led to the widespread use of corticosteroids to reduce the risk of respiratory distress syndrome in pregnant mothers at risk of preterm delivery.[1-5]

At birth, the foetal lung is the most crucial organ for survival. The exact mechanism for the action of corticosteroid is by promoting gas exchange in the foetal lungs. Glucocorticoids causes the reduction of the distance between the blood vessels and the airway, thus providing better exchange of gas in the foetal lungs. It works by reducing the cellular proliferation rates at the mesenchymal tissue therefore reducing the distance for the gas exchange. It also increases the surfactant production and enhances the ability for the airway to remove fluid from the lungs at birth.[6]

There has since been multiple randomized controlled trials and meta- analyses demonstrating the benefits of intramuscular corticosteroids injections in reducing neonatal respiratory morbidities and including intraventricular haemorrhage and necrotizing enterocolitis in preterm infants.[7-11] It is now a recommended practice to administer intramuscular (IM) corticosteroids for pregnancies at risk of preterm delivery.

In 2005, a multicentre pragmatic randomised trial led by Stutchfield first showed that the benefits from IM corticosteroids do extend to term infants undergoing elective

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caesarean section.[12] Since then, a published Cochrane meta-analysis in 2018 combining four randomized controlled trials with a total pool of 3956 patients found that there was significant reduction in respiratory distress syndrome, transient tachypnoea of the neonate, admission to neonatal intensive care unit, admission to neonatal special care for respiratory complications.[12-16]

These randomized controlled trials used the dose for corticosteroids in either of the following regime- IM betamethasone 12mg od 48 hours and 24 hours prior to caesarean section, or IM dexamethasone 2 or 4 doses of 24mg from 48 hours prior to caesarean section or at 37 weeks. [12-16]

The optimal dose for IM corticosteroids and the superiority of individual corticosteroid regime over the other in term infants has not been clearly established.[17] The World Health Organization (WHO) recommended the use of dexamethasone instead of betamethasone as it is more widely available.[19] The 24mg dose for corticosteroids was based on animal studies and appeared sufficient to achieve the steroid concentrations observed in infants after birth during normal physiological stress. The administration of a total dose of 24 mg is most likely the most important for maximal neonatal benefits, but a lower single steroid dose may be useful to reduce maternal side effects, including those in patients with diabetes during pregnancy.[17,18,20,21] A lower dose IM corticosteroids-betamethasone injection has been shown to be beneficial in lab studies and there have also been studies suggesting that the dose of intramuscular corticosteroids should be individualized.[22,25] Additionally, the long-term effects of 24mg corticosteroids administration have not been clearly established. A questionnaire survey follow-up of the trial conducted by Stutchfield et al. suggested that there were no significant association with emotional and academic performance for the children who were given a full course of antenatal corticosteroids prior to caesarean section delivery.[26] However, a recent population-based retrospective cohort study showed that the exposure to a full course maternal antenatal corticosteroid treatment was significantly associated with mental and behavioural disorders in children.[28] It is now no longer recommended in certain centres to give a course of IM dexamethasone prior an elective caesarean section at term. Nevertheless, giving antenatal corticosteroids prior to an elective caesarean section between 37 to 38 weeks is still widely practised in this country.

Therefore, we hope to be able to establish the effectiveness of a lower dose corticosteroids by using a single 12mg IM dexamethasone dose given to mothers antenatally 24 hours prior to having an elective caesarean section. It can limit the unwanted effects of full dose dexamethasone as well as having better compliance in patients. It is thus pertinent to know if any benefit can be derived from a lower dose of IM corticosteroids in reducing neonatal respiratory morbidities and neonatal admissions.

MATERIALS AND METHODS

This was a retrospective observational controlled cohort study of patients undergoing elective caesarean section at 37 weeks to 38 weeks 6 days of gestation and comparing the respiratory morbidities before and after the implementation of 12mg IM dexamethasone in the Obstetrics and Gynaecology Department, Hospital Tuanku Ja'afar (HTJ), Seremban, Malaysia. This study compared two unpaired population sample before and after the implementation of single dose 12mg IM dexamethasone administration to elective caesarean deliveries from 1st July 2019 onwards. The 12mg IM dexamethasone would be administered at least 24 hours before the elective lower segment caesarean section delivery by a trained nurse.

The sampling of the records was done retrospectively according to the inclusion criteria from 1st January 2019 to 30th June 2019, and compared to records from 1st July 2019 to 31st December 2019, records for patients that fulfilled the inclusion criteria will be entered into this study. There were around 880 elective caesarean deliveries performed a year in HTJ therefore, the expected population size is around 880 participants. This study has been registered with NMRR with an ID NMRR-20-2198-54512 (IIR), and with a reference to the document KKM/NIHSEC/P20-2131(10).

Inclusion and exclusion criteria

This study will include patients with singleton pregnancies undergoing elective caesarean section at 37 weeks to 38 weeks 6 days between 1st January 2019 to 31st December 2019.

Under the exclusion criteria, pregnancies that have been diagnosed with foetal congenital malformations or aneuploidy were excluded from the study. Mothers with hypersensivities or were unable to tolerate dexamethasone were excluded. Patients with pre-eclampsia, foetomaternal blood immunization, chorioamnionitis, severely growth restricted foetuses with a birth weight of less than 1.8kg, macrocosmic babies with birth weight of more than 4.5kg, patients who are tested positive for HIV, hepatitis B, hepatitis C or syphilis serology were also excluded from the study. Patients with diabetes in pregnancy on insulin were excluded.

Sample Size

The population for this study was estimated to be around 880 patients undergoing elective caesarean section in a period of one year in HTJ. Therefore, each arm will have around 440 population size. Using a 95% confidence interval with a 5% margin of error from previous studies, the final sample size for each arm should be 205 or higher to give a sufficient representation. This was calculated using Epi InfoTM version 7.2.4.0.

Study outcomes

The study outcomes measured were the rates of respiratory distress syndrome and transient tachypnoea of the newborns; the rates of admission to Neonatal Intensive Care Unit (NICU) and neonatal special care, and the length of stay in the NICU.

We compared the odd ratios and mean of each arm using the Chi- square test and T- test in IBM SPSS version 26. Numerical variables were presented using mean and 95% confidence interval while the categorical variable was presented using odds ratio and their standard deviations (SD).

Table I: Summary comparing the mean age, birth weight, gestational age, and demographics comparison for both groups

	Without dexamethasone (n= 333)	With dexamethasone (n= 341)	P- value
Mean age (years)	33.0 (SD 4.58)	31.7 (SD 4.62)	0.985
Mean birth weight (kg)	2.88 (SD 0.42)	2.91 (SD 0.41)	0.346
Mean gestational age (weeks)	37+2 (SD 4.1 days)	37+3 (SD 2.7 days)	0.211
Demographics:			
Malays	262 (78.7%)	280 (82.1%)	0.261
Chinese	31 (9.3%)	22 (6.4%)	0.168
Indian	30 (9.0%)	28 (8.2%)	0.712
Foreigner	5 (1.5%)	5 (1.5%)	0.970
Other Race	5 (1.5%)	6 (1.8%)	0.792

Table II: Correlation of measured outcomes - for admission to special care nursery, NICU, neonates developing TTN, neonates that required mechanical ventilatory support, and the duration of admission in NICU - with treatment

	Without dexamethasone (n= 333)	With dexamethasone (n= 341)	Odds Ratio (95% CI)	P- value
Admission to special care nursery	29 (8.7%)	30 (8.8%)	0.970 (0.568- 1.656)	0.689
Admission to NICU	15 (4.5%)	14 (4.1%)	0.908 (0.431- 1.911)	0.799
Complications of TTN	28 (8.4%)	27 (7.9%)	1.014 (0.584- 1.760)	0.961
Requiring ventilatory support in NICU	13 (3.9%)	13 (3.8%)	0.976 (0.445- 2.137)	0.951
Duration of admission in NICU (Mean, SD)	1 week 1 day (SD 8 days)	5 days (SD 2 days)		0.172

NICU= Neonatal Intensive Care Unit; TTN= Transient Tachypnoea of the Newborn

Table III: Summary of the measured outcomes for maternal age group below 35-year-old

	Without dexamethasone (n= 233)	With dexamethasone (n= 255)	Odds Ratio (95% CI)	P- value
Admission to special care nursery	17 (7.8%)	21 (8.2%)	1.056 (0.542- 2.057)	0.873
Admission to NICU	13 (6.0%)	9 (3.53%)	0.619 (0.260- 1.477)	0.276
Complications of TTN	18 (8.3%)	17 (6.7%)	0.853 (0.429- 1.698)	0.651
Requiring ventilatory support in NICU	11 (5.1%)	10 (3.9%)	0.823 (0.343- 1.977)	0.663
Duration of admission in NICU (Mean, SD)	1 week 2 days (SD 9 days)	6 days (SD 2.5 days)		0.198

Table IV: Summary of the measured outcomes for maternal age group 35-year-old and above

	Without dexamethasone (n= 100)	With dexamethasone (n= 86)	Odds Ratio (95% CI)	P- value
Admission to special care nursery	13 (13%)	10 (11.6%)	0.881 (0.365- 2.123)	0.777
Admission to NICU	2 (2%)	3 (3.5%)	1.770 (0.289- 10.854)	0.531
Complications of TTN	9 (9%)	11 (12.8%)	1.483 (0.584- 3.768)	0.405
Requiring ventilatory support in NICU	2 (2%)	3 (3.5%)	1.771 (0.289- 10.854)	0.531
Duration of admission in NICU (Mean, SD)	1 week (SD 3.9 days)	6 days (SD 2.0 days)		0.580

RESULTS

There were 883 patients who underwent elective caesarean section in 2019. A total of 674 patients fulfilled our study criteria and was entered into our analysis. The commonest reason for exclusion in both groups was infants born to mothers with diabetes in pregnancy requiring insulin, as their newborns will require routine admission and observation in the neonatal special care for hypoglycaemia. There were 74 in the control and 68 in the treatment arm for patients who required insulin antenatally. The second commonest reason for exclusion was being beyond the studied gestational age during the caesarean section delivery. The flow chart for patient recruitment is outlined in Figure 1. The commonest indication for the elective caesarean section for both groups was having multiple previous caesarean section.

Table I shows that both groups of the study were comparable with no significant differences for the mean age, birth weight, gestational age, and demographic distribution. Therefore, there was no significant evidence of bias between the two groups. Table II summarizes the measured outcomes between the group that were given dexamethasone and the control group, without the dexamethasone injection.

As the SD for the mean age in both groups crosses 35-year-old therefore, we have done an additional analysis on the measured outcomes in different age groups, ≥35-year-old and <35-year-old. We tabulated these findings in Tables III and IV. Table III shows the summary of the measured outcomes for admission to special care nursery, NICU, rate of TTN, the need for mechanical ventilation, duration of admission in NICU with their respective p- values for maternal age group below 35-year-old whilst, Table IV shows these measured

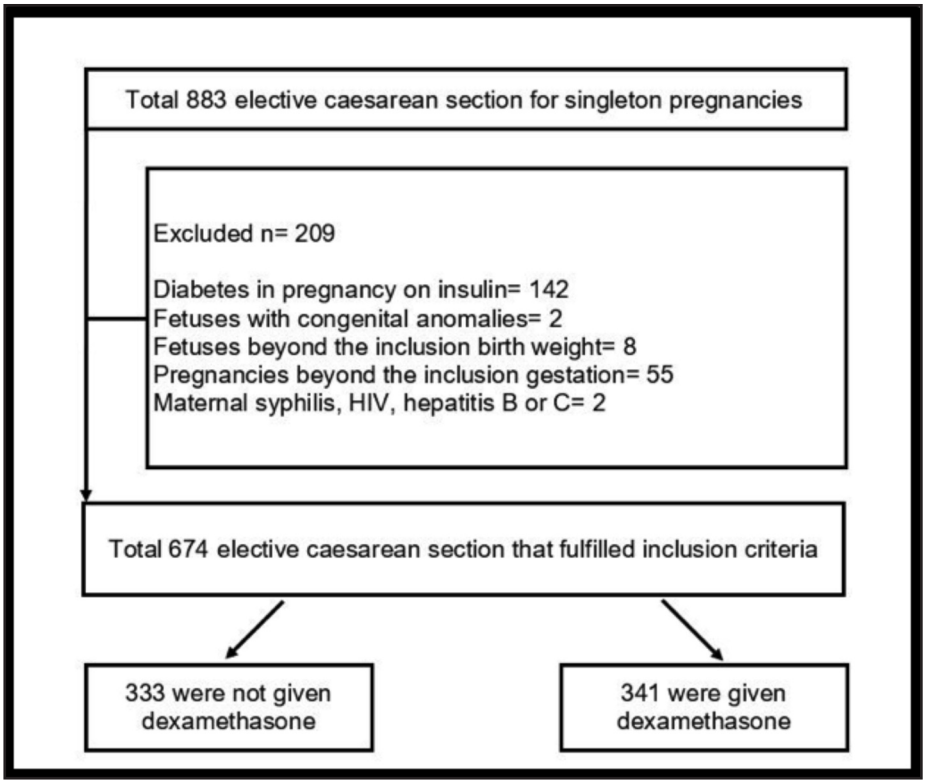

Fig. 1: Flow chart showing the participants excluded from this study.
N.B. HIV= Human Immunodeficiency Virus.

outcomes for maternal age group 35-year-old and above. The control and intervention group in both age groups were comparable with no significant differences in age, birth weights, gestational ages, and distribution of demographics. The results showed no significant differences when the age groups were separately analysed.

DISCUSSION

Caesarean section deliveries done before 39 weeks have a higher risk for transient tachypnoea of the newborn, respiratory morbidities and neonatal asphyxia compared to a vaginal delivery.[23,24,29] The rate of respiratory morbidities for caesarean section done at 39 weeks and beyond are not significantly different from vaginal deliveries but, it has a slight increased risk of antepartum stillbirth of around 0.05%. Therefore, it is recommended that consideration should be given for antenatal corticosteroids prior to an elective caesarean section before that gestation of 39 weeks.[29] For elective caesarean section done at 39 weeks and beyond, there is a high possibility that patients may present in labour before their planned caesarean section date and may end up requiring an emergency caesarean section which carries a higher risk of haemorrhage and hysterectomy.[23] Therefore, this study only included elective caesarean section done between 37 weeks to 38 weeks 6 days as their rate for respiratory morbidity is higher compared to caesarean section deliveries at 39 week and beyond.

The dose for the IM corticosteroids was derived from studies done more than half a century ago. There have not been much changes to the dosage and timing used for both drugs-betamethasone and dexamethasone.[25] The WHO recommends the use of dexamethasone as it is more widely available and more affordable particularly in countries with low resources.[19] Recent lab-based studies have demonstrated that lower doses of corticosteroids may be as effective and it can reduce unnecessary foetal exposure to the drug.[22,25] There have also been published papers suggesting that an individualized dose of antenatal corticosteroids may be needed to reduce neonatal respiratory morbidities.[27] Therefore, it was intended for our study to demonstrate benefits from a lower dose of antenatal corticosteroids whilst minimizing foetal exposure.

In our study, there was a total of 29 admissions to NICU in both groups studied, the commonest reason for admission to the NICU was transient tachypnoea of the newborns requiring mechanical ventilation, there were 11 neonates who were given this diagnosis, of which five were from the control group and six were from the treatment group. The second common reason for admission was congenital pneumonia which involved seven neonates, five of which were from the treatment group and 2 from the control group. These neonates showed radiological evidence of pneumonia which required resuscitation, intravenous antibiotics, and mechanical ventilation. Ventilatory support in the form of Continuous Positive Airway Pressure (CPAP) or Duo Positive Airway pressure were required in 13 neonates of each group.

There were 15 admissions (4.5%) to NICU in the control group, and from these admissions there was one early

neonatal death after three days of birth, the cause of death was due to severe congenital pneumonia with persistent pulmonary hypertension of the newborns. There was no post-mortem done for this case and there was also no routine anomaly scan done for the pregnancy during the antenatal period. We were therefore unable to exclude this case based on our inclusion criteria for any foetal abnormalities. There was also a neonate that developed congenital pneumonia in the control group requiring ventilation for 11 days and eventually developing complications of recurrent pneumothorax. This was the longest duration of neonatal ventilation required in the studied population. Eventually, this neonate recovered and was discharged after 30 days of admission. Apart from these two cases, the other neonates in the studied population that required ventilation recovered uneventfully without additional complications.

There were no patients documented to have developed acute reaction to the single dose intramuscular dexamethasone given. The rates of admission to neonatal special care for an elective caesarean section were 8.7% in the control group and 8.8% in the group given dexamethasone. The commonest reason for these admissions was transient tachypnoea of the newborn.

Our results showed that a lower dose IM dexamethasone did not achieve similar outcomes as the higher dose dexamethasone injections. This may be due to insufficient levels of dexamethasone in the foetal lung circulation to induce the secretion of surfactants during the time of delivery compared to betamethasone that has a longer half- life. Dexamethasone has a shorter half-life compared to betamethasone, therefore injecting the dexamethasone nearer to the time of delivery, perhaps just 12 hours or to give the injection in two separate doses of 6mg just before the planned Caesarean section may have demonstrated a clinical benefit in this study.[30,31] Additionally, in order to test for a therapeutic drug benefit, a larger randomized controlled trial with such dose would have been more appropriate only if the ethical approval is granted for such study.

Among the strength of this study was that we excluded pregnancies with maternal conditions such as diabetes on insulin, maternal syphilis, HIV, hepatitis B or C from the study population, as well as foetal anomalies and foetuses with extremes of birth weight, all of which had been poorly mentioned in previous studies. These conditions would have warranted routine admissions to special care nursery and would not have shown any possible benefit from antenatal corticosteroids injection.

Limitations of the study

One of the weaknesses found in this study was that there were a few admissions to the special care nursery, which was unrelated to respiratory morbidities, for instance a laceration wound to the foetal scalp, or hypothermia. Nevertheless, such admissions were rare and would not have affected the statistical analysis of our findings.

CONCLUSION

This study showed that there were slightly lower rates for neonatal admissions to NICU, special care nursery and the need for mechanical ventilation as well as the duration of admission in NICU when 12mg dexamethasone was given however, no statistically significant differences were demonstrated for these findings. The use of such dexamethasone should only be a viable option in a research setting. From this study, there was insufficient evidence to recommend a lower dose antenatal corticosteroid prior to an elective caesarean section for the purpose of reducing respiratory morbidities and considering that there have been long term harmful consequences demonstrated from the higher dose of antenatal corticosteroids exposure at term, this practice should therefore be discontinued until larger studies are done to refute these findings.

CONFLICT OF INTEREST

None declared

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