

H.C.G (Human Chorionic Gonadotropin) versus Magnesium sulphate in suppression of preterm labour

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Abstract

Introduction: Preterm labour is a major healthcare problem throughout the world, it is a major cause of perinatal mortality and morbidity. **Methods:** Prospective comparative study conducted in the Department of Obstetrics & Gynaecology at Kamla Raja Hospital, Gwalior, M.P, from August 2011 to September 2012. Sample Size: 80. 50 patients were given H.C.G. and 30 were given Magnesium sulphate to suppress preterm labour. Statistical analysis done using Chi square test in SPSS software and p value < 0.05 was considered significant. **Results:** Mean duration between initiation of treatment & suppression of contractions was 3.1 hrs & 2.9 hrs in women receiving H.C.G. & Magnesium sulphate respectively (p value<0.0001). Mean prolongation of pregnancy was 31.4 days and 30.33 days in women receiving H.C.G. & Magnesium sulphate respectively (p value = 0.78). Average rate of labour within 48 hrs after beginning of treatment was 8% and 6.67%, in H.C.G. & Magnesium sulphate grp respectively, p value=0.43. None of the women receiving H.C.G. had any side effects, all 30 women receiving Magnesium sulphate had minor maternal side effects, p value (<0.0001). Mean birth weight was 2.35 kgs and 2.19 kgs respectively in women receiving H.C.G. and Magnesium sulphate repectively, (p value = 0.22). **Conclusion:** Magnesium sulphate is better tocolytic drug, showing statistically significant lesser time between the initiation of treatment & suppression of contractions, as compared to H.C.G. Women receiving Magnesium sulphate suffered from minor side effects; however those treated with H.C.G. had no complaints.

Key words: Human chorionic gonadotropin, Magnesium Sulphate, Preterm Labour, Tocolytic.

Introduction

American college of obstetrics & gynaecology (ACOG) in 1995 has defined preterm labour as labours which take place after 20th week and before 37th week of pregnancy. Preterm labour constitutes about 10% of total labours, but since 70 % of infant mortality is due to this, this problem is considered as one of the international indices in assessment of health condition worldwide [1].

Any preterm birth postponed by more than 48 hrs helps to administer glucocorticoids to the mothers, for acceleration of fetal lung maturation and reduction of risks of neonatal intraventricular haemorrhage and necrotizing enterocolitis, thereby reducing neonatal morbidity and mortality. This also gives clinicians time

to refer mothers to a better and modern centre possessing neonatal intensive care unit (NICU). Various treatments have been employ to suppress preterm labour by reducing uterine contraction [1,2].

Human Chorionic Gonadotropin (H.C.G.) is a heterodimeric glycoprotein produced primarily in the placenta and has multiple endocrine, paracrine and immunoregulatory actions [3]. The importance of H.C.G. in maintenance of early pregnancy has been widely accepted, reports have highlighted a potential role of H.C.G. in maintaining uterine quiescence in the third trimester. H.C.G. exerts a potent concentration dependent inhibitory effect on human myometrial contractions [4]. The H.C.G. receptors in human myometrium are downregulated following the onset of labour, in both term and preterm deliveries [3,4]. H.C.G. in vitro acts by a type of mechanism connected to gas that can activate the plasma membrane of

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adenylate cyclase, thereby reducing specific gap junctions of myometer cells and eventually decreasing surface tension of intracellular calcium, thus keeping myometer in zero phase of labour and causing uterine relaxation [5]. The power of H.C.G. in suppression of preterm labour might be due to direct restraint of myometer responses by production of eicosanoids. H.C.G. induces the production of eicosanoids, that are similar to prostacyclines, that immediately causes loosening of myometer muscles [6]. Recent data suggest that H.C.G. might have a role as endogenous tocolytic agent in normal pregnancy. A significant decrease in serum H.C.G. levels was found 2 -3 weeks before the spontaneous onset of labour. This might contribute to increasing the contractility in the uterine muscle and gradually initiating the onset of labour [7].

Following I.M. injection, peak concentration of H.C.G. occurs about 6 hrs after a dose. It is distributed primarily to gonads. Blood concentration declines in a biphasic manner, with a half life between about 6 and 11 hrs and 23 to 38 hrs respectively. About 10 to 12% of an intramuscular dose is excreted in urine within 24 hours [8].

Magnesium sulphate has been used since 1960 in the United States as a tocolytic agent [9]. Magnesium ions suppress myometrial contractions by obstruction of calcium canals. But some randomised studies have shown that Magnesium sulphate is as effective as placebo in suppressing preterm labour [9,10].

When Magnesium sulphate is used in treatment of preterm labour, it can cause symptoms like nausea, vomiting, hyperthermia, and hypotension and in some cases acute pulmonary oedema and respiratory failure. As a result of passage of magnesium ions into placenta different neonatal complications including muscular atony and restlessness are inevitable [11].

In our study we compare the efficacy as well as side effects profile of these two tocolytic agents.

Material and Methods

This study was a prospective comparative study conducted in the Department of Obstetrics & Gynaecology at Kamla Raja Hospital, Gwalior, M.P., from August 2011 to September 2012.

Sample Size: 80

After taking approval from the ethical committee, G.R.M.C., Gwalior, M.P., 50 women were given Human Chorionic Gonadotropin (H.C.G.) and 30 were given Magnesium sulphate.

Inclusion criterias were: 4 uterine contractions per 20 min or 8 contractions per hour, live single fetus, pregnancy less than 37 weeks, intact membranes, dilatation less than 3cm and effacement less than 80%.

Exclusion criteria were: abnormal vaginal bleeding, ruptured membranes, uterine anomalies, diagnosed congenital anomaly in the fetus, maternal infections, chorioamnionitis, maternal heart disease, APH, diabetes, preeclampsia, eclampsia or gestational hypertension, fetal disorders like fetal distress, IUGR, Polyhydraminos etc. and dilatation more than 3 cm.

Gestational age was determined by last menstrual period and first trimester ultrasound dating. Informed written consent was obtained from all the patients.

All patients were admitted in labour room and their Haemoglobin concentration, urinalysis and microscopical examination, blood group and Rh, blood sugar was done. In order to speed up fetal lung maturation, Betamethasone 12mg every 24 hrs was prescribed for two days. In order to prevent any streptococcal infection in neonates in both group 2gm of iv ampicillin was given stat followed by 6hrly injections.

50 women were given H.C.G. (Human Chorionic Gonadotropin), in a dose of 5000 units i.m. injection, followed by a drip of 10000 units in 500ml of normal saline at the rate of 20 drops per minute. Half hourly assessment of uterine contractions, maternal vital signs, fetal heart rate monitoring was done.

30 women were given an initial loading dose of 4 gms of Magnesium sulphate i.e. 4 ampoules of 50 % Magnesium sulphate dissolved in 20 ml of 5% dextrose, given intravenously slowly over 5-10 min. This was followed by 4 gm Magnesium sulphate in 500cc of 5% dextrose every 8 hrly, till the symptoms of preterm labour subsided or any unacceptable side effect occurred. Half hourly assessment of B.P., maternal breathing, deep tendon reflexes, maternal urine output, fetal heart rate was done. Efficacy was determined by observing subsidence of uterine contractions, FHS, Respiratory rate of mother at least 14/min, Urine output of more than 30 ml/hour, presence of deep tendon

reflexes. Also, if patient had any complaint due to drug related side effects, it was duly noted.

Patient was kept under observation 24 hrs after cessation of uterine contractions and arrest of labour. Follow up was performed in antenatal clinics. At each visit blood pressure, pulse rate and fetal heart rate were recorded. Signs and symptoms of preterm labour were reviewed. At the time of delivery, neonatal weight and

weeks of gestation were determined to calculate duration of prolongation of pregnancy. Tocolysis was considered successful when contractions ceased and delivery was delayed by 48 hrs.

Statistical analysis as done using chi square test in SPSS Software and p value < 0.05 was considered significant.

Results

The results of our study indicate that the demographic characteristics in both the study groups were similar, including maternal age, parity, gestational age, education and socioeconomic factors.

Mean maternal age in our study was 24.85 yrs. 41 out of 80 patients (51.25%) belonged to the age group 20-25 yrs. (Table 1)

Table No. 1: Distribution of cases according to maternal age

Age (yrs)	H.C.G. (n=50)	MgSO4 (n=30)	Total	
			No.	%
< 20	4 (8%)	3 (10%)	7	8.75
20-25	25 (50%)	16 (53.33%)	41	51.25
26-30	15 (30%)	8 (26.67%)	23	28.75
> 30	6 (12%)	3 (10%)	9	11.25

It is evident from the above table that maximum patients belong to the age group 20-25 yrs.

Mean parity in our study was 1.01. Maximum patients in our study were nulliparous (29 out of 80; 36.25%).

Mean gestational age at the time of enrollment was 31.22wks & 30.93wks, in women receiving H.C.G. & Magnesium sulphate respectively. Maximum cases were enrolled between gestational ages 30-31 wk 6days i.e. 36.25%. (Table 2)

Table No. 2: Distribution of cases according to gestational age

Gestational age	H.C.G. (n=50)	MgSO4 (n=30)	Total	
			No.	%
< 28 wk	4 (8%)	2 (6.66%)	6	7.5
28-29 wk 6 days	8 (16%)	5 (16.67%)	13	16.25
30-31 wk 6 days	18 (36%)	11 (36.67%)	29	36.25
32-33 wk 6 days	15 (30%)	9 (30%)	24	30
34-37 wk	5 (10%)	3 (10%)	8	10

According to the above table maximum number of patients studied belonged to the gestational age 30-31 wk 6 days i.e. 36.25%.

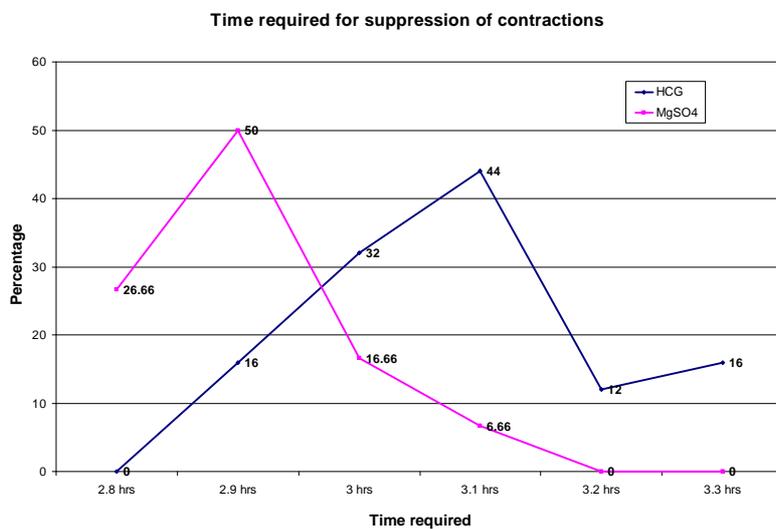
Most of the patients presented with the complains of pain, backache and white discharge PV (34 out of 80: 42.5%). After initiation of tocolytic treatment, time required for suppression of contractions was noted. Mean duration between initiation of treatment and suppression of contractions in H.C.G. group was 3.1 hrs and in Magnesium sulphate group was 2.9 hrs (**p value < 0.0001: statistically significant**), indicating more rapid onset of tocolytic action of Magnesium sulphate. (Table 3, Figure I)

Table No. 3: Time required for suppression of contractions (hours)

Time required (hours)	H.C.G. (n=50)	MgSO4 (n=30)
2.8	0 (0%)	8 (26.66%)
2.9	8 (16%)	15 (50%)
3	6 (32%)	5 (16.66%)
3.1	22 (44%)	2 (6.66%)
3.2	6 (12%)	0 (0%)
3.3	8 (16%)	0 (0%)

Mean time required for suppression of contraction in H.C.G. was 3.1 hours and in Magnesium Sulphate group was 2.9 hours.(p value <0.0001 ; highly significant)

Figure 1



Mean prolongation of pregnancy in H.C.G. group was 31.4 days & in Magnesium sulphate group was 30.33 days (p value = 0.78; statistically non significant), implying both these drugs have similar efficacy with respect to mean prolongation of pregnancy. Average rate of labour within 48 hrs after beginning of treatment, in the H.C.G. group was 8%(4 out of 50) and in the Magnesium sulphate group was 6.67%(2 out of 30); p value =0.43: statistically non significant. (Table 4)

Table No. 4: Distribution of cases according to no. of days prolonged after initiating treatment

No. of days prolonged	H.C.G. (n=50)	MgSO4 (n=30)
< 2	4 (8%)	2 (6.67%)
2	0 (0%)	0 (0%)
3-6	5 (10%)	2 (6.67%)
7-13	2 (4%)	2 (6.67%)
14-20	1 (2%)	6 (20%)
≥ 21	38 (76%)	18 (60%)
Total	50	30

After initiating treatment, more than 21 days were prolonged in 38 out of 50 patients (76%) in women receiving H.C.G. and in 18 out of 30 patients (60%) in women receiving Magnesium Sulphate. Mean days prolonged were 31.4 days and 30.33 days respectively in H.C.G. and Magnesium sulphate group (p value < 0.78, not significant).

Prolongation of pregnancy was maximum when the tocolytic treatment was initiated in women between 28-29wk6days gestational age, with the mean prolongation of 40.75 days and 41.4 days in H.C.G. & Magnesium sulphate group respectively. (Table 5)

Table No. 5: No. of days prolonged wrt gestational age at the initiation of treatment

Gestational age	Days prolonged (Mean \pm S.D).	
	H.C.G.	MgSO4
< 28 wk	38.75 \pm 26.53	39.5 \pm 0.71
28-29 wk 6 days	40.75 \pm 17.40	41.4 \pm 22.63
30-31 wk 6 days	34.16 \pm 14.13	33.90 \pm 17.79
32-33 wk 6 days	24.66 \pm 11.59	24.20 \pm 10.91
34-37 wk	20.8 \pm 24.79	11 \pm 4.36

Maximum days were prolonged when treatment was started at 28-29 weeks 6 days gestational age implying that earlier we start the treatment, better it is.

None of the patients receiving H.C.G. had any complaints. All 30 women receiving Magnesium sulphate had one or another complaints from side effects of drugs. This is a **statistically significant difference, p value <0.0001.** (Table 6)

Table No 6: Table showing side effects of HCG and MgSO4

Side effects	HCG (n=50)	MgSO4 (n=30)
Headache	0 (0%)	8 (26.67%)
Dizziness	0 (0%)	8 (26.67%)
Thirst	0 (0%)	18 (60%)
Nausea and vomiting	0 (0%)	9 (30%)
Hyperthermia	0 (0%)	15 (50%)
Headache + Nausea	0 (0%)	6 (20%)
Headache + Hyperthermia+Vomiting	0 (0%)	6 (20%)

Maximum newborns weighted in the range of 1.5-2.5 kgs (68.75%).The mean birth weight of babies delivered by the patients included in our study were 2.35 kgs and 2.19 kgs, amongst women receiving H.C.G. and Magnesium sulphate respectively, p value = 0.22; statistically non significant. Babies born to mothers showed no adverse side effects.

Different variables studied in this study are compared and p values quoted in **Table 7.**

Table No. 7: Comparison of variables in two groups: H.C.G. & Magnesium sulphate

Variables	H.C.G.	Magnesium sulphate	p value
Maternal age (yrs)	24.96	24.67	0.713
Gestational age (wks)	31.22	30.93	0.344
Time between start of drug & suppression of ontractions(hrs)	3.1+ \pm 0.129	2.9+ \pm 0.085	<0.0001
Labour within 48hrs	8%	6.67%	0.431
Complaints of patients	0%	100%	<0.0001

Discussion

The present study indicates that the ability of H.C.G. in suppression of preterm labour is similar to Magnesium sulphate, except for the time between initiation of treatment & suppression of contractions. Magnesium sulphate takes statistically significant lesser time between initiation of treatment and suppression of contractions. Minor maternal side effects were seen in 100% of patients receiving Magnesium sulphate while nil for H.C.G. None of these side effects were severe enough to cause discontinuation of treatment. No fetal side effects were seen with both the drugs.

Magnesium sulphate has been used since 1960 in the United States in obstetrics for treatment of preterm labour and randomised clinical trials have shown it to be as effective as placebo for the same [9,10].

Magnesium sulphate is found to be a successful, inexpensive and relatively non-toxic tocolytic agent that has few side effects [12].

Magnesium sulphate has a definite role in fetal neuroprotection. Doyle and coworkers in the Cochrane review concluded that antenatal Magnesium sulphate therapy given in women at risk of preterm birth substantially reduces the risk of neonatal cerebral palsy. There was significant reduction in the rate of substantial gross motor dysfunction^[13]. RCOG has concluded that Magnesium sulphate given to mothers shortly before delivery reduces the risk of cerebral palsy & protects gross motor function in those infants born preterm [14].

Carlos et al, observed that H.C.G. may play a significant role in maintaining pregnancy well after first trimester. Mechanism of action of H.C.G. in treatment of threatened abortion is reduction of resistance against arterial blood flow [15,16].

Slattery et al, demonstrated that H.C.G. exerts a significant concentration dependent relaxant effect on human myometrial tissues in the third trimester of pregnancy [4].

Kurtzman et al reported the role of H.C.G. in maintenance of early pregnancy and its role in the maintenance of the later stage of pregnancy, by directly and indirectly promoting uterine quiescence. As an endogenous tocolytic, H.C.G. may be an ideal candidate for the therapy of preterm labour [17].

Ali et al, observed the mean prolongation of 28.8 days in H.C.G. treated group versus 15 days in placebo treated group, which was statistically significant difference between the two groups (p value < 0.001), thus concluding that it exhibits potent tocolysis with no fetal side effects, when compared to placebo [18].

Ibtissam Youssif AL Saffar et al conducted a study, using H.C.G., on 57 women with preterm labour in Baghdad, Iraq from April 2006 till November 2006 and concluded that H.C.G. exhibits potent tocolysis, thereby prolonging pregnancy durations in women with preterm labour, without causing any adverse maternal/neonatal side effects [19].

Sakhavar N et al in their clinical trial study "Magnesium sulphate versus H.C.G. (Human Chorionic Gonadotrophin) in suppression of preterm labour" conducted on 64 women in Iran showed both the drugs to have similar efficacy. The average duration between initiation of treatment and suppression of contractions in their study showed non-significant difference between the two drugs, p value = 0.132 [20].

Lorzadeh N et al., in their study found that delivery was delayed for 48 hrs in 90.3% of women receiving H.C.G. The mean birth weight in their study was 2334 gm, which is almost similar to that found in our study. No adverse maternal/neonatal side effects were observed by them [21].

Difference between our study and previously conducted studies is that we have obtained statistically significant difference between the two drugs with respect to initiation of treatment & suppression of contractions, implying Magnesium sulphate as a more rapidly acting tocolytic drug.

Conclusion

Both Magnesium sulphate and H.C.G. have similar tocolytic efficacy in suppressing preterm labour, however Magnesium sulphate is better than H.C.G., as it has statistically significant, faster onset of action. Magnesium sulphate is a successful, inexpensive and relatively non-toxic tocolytic drug and has a definite role in fetal neuroprotection. Patients given Magnesium sulphate suffered from minor maternal side effects, none of which required treatment discontinuation. Further studies are needed to establish role of H.C.G. in premature labour.

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