Original Article

Comparison of Heparin and Low Dose Aspirin with Low dose Aspirin Alone in Improving the Perinatal Outcome in Pregnancies with Recurrent Pregnancy Losses

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Abstract

Objective:To compare the perinatal outcome of low dose Aspirin (LDA) alone and low dose Aspirin with Heparin in pregnancies with recurrent pregnancy loss (RPL) with or without positive antiphospholipid antibodies (aPL).

Study Design: Randomized controlled trial.

Setting: Departments of Obstetrics and Gynaecology Combined Military Hospital (CMH) Quetta, Lahore and Rawalpindi.

Duration of Study:30 April 2009 to 30 April 2011.

Methodology:60 women with recurrent pregnancy losses (RPL) fulfilling clinical criteria of antiphospholipid syndrome (APS) with or without aPL antibodies positive reporting to the antenatal clinic at the three hospitals were included. Convenience sampling was done and subjects were randomly allocated into groups A and B using random numbers table.

GroupA received low dose Aspirin(LDA) 75 mg once daily starting from first trimester and GroupB received unfractioned Heparin (UH) 5000IU SC BD or low molecular weight Heparin (LMWH) 40mg subcutaneous along with LDA .

Results: In group A 26(86.7%) and in group B 25(83.3%) live births were attained. Significant side-effects were observed in groupB including bruising and injection site pain. Cost of drug for treatment over 28 weeks in groupA was Rs 300 and in groupB was Rs 6300.

Conclusion: LDA alone have comparable perinatal outcomes with Heparin in cases of RPL, with an added benefit of no pain and bruising, low cost and more convenience of administration.

Key Words: Intrauterine death, Recurrent miscarriage,Antiphospholipid Syndrome,Bad Obstetric History,Low dose aspirin, Low molecular weight heparin.

Introduction

Antiphospholipid antibodies are a heterogeneous family of auto-antibodies directed against phospholipids binding plasma proteins. The two most clinically significant are the lupus anticoagulant (LA) and the anticardiolipin antibodies (aCL). The combination of either of these with one or more of the characteristic clinical features is known as Antiphospholipid syndrome.[1]

Antiphospholipid syndrome as originally defined refers to association of persistently positive titres of LA or aCL with either arterial or venous thrombosis or recurrent miscarriages or thrombocytopenia.[2] The current obstetric criteria is defined as the history of one or more IUD >10 weeks of morphologically normal fetus, one or more preterm birth <34 weeks associated with PET, Eclampsia or severe placental insufficiency or three or more consecutive miscarriages <10 weeks (Table I). APS is present if at least one of the clinical criteria and one of the lab criteria are met.[3]

Since hypercoagulability increases chances of compromised obstetric outcomes anticoagulant agents could potentially increase the live birth rate in subsequent pregnancies.[4]In the past few years there has been an increasing interest in the relationship between APS and anticoagulants as low dose aspirin (LDA) and heparin in management of adverse pregnancy outcomes.

It is not unusual to find cases of recurrent miscarriages, early onset severe PET and unexplained intra-uterine deaths in our obstetric population, which very well fulfill the clinical criteria of APS but fulfilling the laboratory criteria for APS is associated with a lot of practical difficulties. A variety of assays and instruments are used to detect the same antiphospholipid antibody; and finally longitudinal studies report that the titres of aPL fluctuate over time.[5] No single test will detect all antibodies and ideally a panel of assays should be performed. Individuals may have transiently positive tests which are not thought to be of clinical significance.[6]It is also imperative to test for both LA and aCL as there is little cross over between positivity for one aPL and another.[7] And then all tests results should be confirmed on a repeat sample taken at least 06 weeks later.

Despite the limitations of laboratory analysis Low dose Aspirin with or without Heparin is being increasingly used in our country in cases with recurrent pregnancy losses (RPL). Heparin administration involves exhaustive counselling, careful follow-up and inconvenience of administration. Over and above cost of treatment over 6 to 7 months being much higher than LDA alone.

This study was planned to investigate whether LDA alone is as effective in improving the peri-natal outcome as Heparin and low dose Aspirin in selected cases of RPL fulfilling criteria of APS associated obstetric morbidity, which are not necessarily fulfilling

laboratory criteria of positive anti-phospholipid antibodies.

Methodology

Using prevalence of recurrent pregnancy losses of 3% (8) at 95% Confidence interval and 80% power, required sample is 45. We included 60 patients, 30 in each group. Patients were included through convenience sampling and randomly allocated into two groups using random numbers table. Thirty pregnant women at gestational age <10 weeks fulfilling the APS clinical criteria (Table I) were recruited in each group after informed consent from Obstetric unit of CMH Quetta, Lahore and Rawalpindi from April 2009 to April 2011.

Ethical approval was obtained from the hospital ethical committee after submitting the detailed research proposal. Trial was initially planned as a double blind randomised controlled trial. But the ethical committee did not approve the administration of placebo injections to women for 28-30 weeks. Blinding was therefore omitted and the methodology was modified accordingly.

One hundred and forty seven cases were screened as RPL on the basis of risk scoring in antenatal clinic. Excluding 53 cases with positive history of fetal dysmorphology, true knot, abruption without hypertension, true preterm labour unassociated with PET and obstetric cholestasis, investigations including TORCH screen, VDRL, HbA1C,Klie-Haur test (regardless of blood group), Anti Ro antibodies were sent for rest of the 54 cases. All those found positive were excluded. Selected 60 patients were otherwise asymptomatic with no other co-morbidities.

Only patients less than 10 weeks pregnancy with history of one or more IUD >10 weeks of morphologically normal fetus, one or more preterm birth <34 weeks associated with PET, eclampsia or severe placental insufficiency or three or more consecutive miscarriages <10 weeks, with or without initial positive anticardiolipin antibodies were included in the study. The patients were randomized at single site by the principal investigator. Patient'sup to 10-11 weeks were enrolled i.e. before the first wave of trophoblast invasion.

Thirty women after taking informed consent of the couple were commenced on 75 mg aspirin once daily as soon as pregnancy test was positive in group A and for group B additional heparin 5000 IU SC BD/ 40 mg Clexene OD (depending upon the socio-economic status of the woman) was commenced once fetal cardiac activity was positive on transvaginal scan. Initially group B was admitted for training purpose for subcutaneous injection administration but later therapy was continued as outdoor. A baseline and then at 2-4 weeks platelet count was checked to screen for thrombocytopenia, a rare side-effect of heparin administration.

Women were followed up fortnightly during the first trimester in early pregnancy. Formal anomaly scan by consultant radiologist was carried out at 22 weeks of gestation.

Outpatient monitoring continued with fortnightly checkups till 34 weeks and weekly there-after. Growth scans were carried out at 28 and 32 weeks with amniotic fluid index calculation (AFI). Umbilical Artery Doppler Indices (UADI) were only indicated if there were concerns of growth restriction or oligohydramnios.

Perinatal alert was raised in all cases and all patients were delivered at hospital with tertiary neonatal care facilities.

Aspirin was stopped at 36 weeks and Heparin was continued till patient went in labour or 24 hours before elective surgery/induction of labour (IOL) was planned.

Decision regarding the time and mode of delivery was influenced only by obstetric reasons. Considering the high risk history none of the pregnancies was allowed to proceed beyond 40 weeks (EDD was calculated on the basis of booking scan).

Results

Data was analyzed using SPSS version 17. Descriptive statistics were used to describe the data i.e. mean and standard deviation (SD) for quantitative while frequency and percentages for qualitative variables. Quantitative variables were compared through independent samples't-test and qualitative variables were compared through chi-square test between both the groups. p value < 0.05 was considered as significant.

Comparing the demographics and past history the groups were comparable. All patients were in reproductive age group with mean age in groupA as 27 ± 2.5 years and in group B it as 28.5 ± 3.46 years (p value= ns). Regarding past history in group A 12(40%) while in group B 18(60%) patients had recurrent miscarriages (RM) (p value=ns) while rest had suffered a combination of RM and late fetal demise (fetal death after 24 weeks of gestation). In group A 22 (73.7%) and in group B 24(80%) cases had no live issue (p value= ns) despite being married for ≥ 5 years (Table II).

The study may be criticized for inclusion criteria being wide and inclusive of losses at all gestations. Under ideal circumstances, such trials should have had stratification for those having RM and late fetal demise and those having recurrent abortions only, and then have randomization between control and experimental group within each stratum and have a subgroup analysis. But our trial was based on use of anticoagulants targeting uteroplacental insufficiency and thus our inclusion criteria was strictly confined to RM and those late fetal losses (intra-uterine death) which were fulfilling the obstetric criteria of APS (Table I) and where such pathology is suspected to compromise both early and late fetal outcomes.

Table I. Comparison of demographic and past history between both the groups

Patients characteristics	Group A (n = 30)	Group B (n = 30)	p value
Age (years)	27.07 ± 2.50	28.10 ± 3.46	0.190^{NS}
Gestation Age (Weeks)	10.4 ± 3.34	11.1 ± 2.68	0.374^{NS}
Losses			
Recurrent Miscariage	12 (40%)	17 (56.7%)	0.602^{NS}
Recurrent Miscariage + IUD	18 (60%)	13 (43.3%)	
Alive Babies			0.542^{NS}
< 1	22 (73.3%)	24 (80%)	
≥ 1	8 (26.7%)	6 (20%)	

NS = not significant

Anticardiolipin antibodies (IgG) were positive at 2 intervals 06 weeks apart in 5 cases in each group. Both LA and aCL were positive only in 3 cases in group A and 5 cases in group B, while none of antiphospholipid antibodies were detected in 18 cases in group A and 14 cases in group B (p value = ns).

Mean gestational age at booking was 10.4 weeks in group A and 11.1 weeks in group B.

Table II. Comparison of Perinatal Outcome between both the groups

Patients characteristics	Group A (n = 30)	Group B (n = 30)	p value
Outcome			
Live Births	26 (86.7%)	25 (83.3%)	0.718^{NS}
Miscarriages	3 (10%)	4 (13.3%)	
IUD	1	1	
Preterm			
≥ 37 weeks	22 (73.3%)	24 (80%)	0.542^{NS}
>37 weeks	8 (26.7%)	6 (20%)	
IUGR/ Oligo	3 (10%)	5 (16.7%)	0.448^{NS}
APGAR score at birth	8.53 ± 0.507	8.60 ± 0.498	0.610 ^{NS}
Birth weight (kg)	3.0 ± 0.135	3.1 ± 0.114	0.068 ^{NS}
CS Rate	18 (60%)	22 (73.3%)	0.273^{NS}

Growth Scan was performed at 28 to 32 weeks and showed a steady increment in biometric features for both the groups. There were only 3(10%) cases in group A and 5 (16.7%) cases in group B (*p value* =ns) where IUGR with reduced AFI (<5th centile) was noted and delivery was attained at ≤35 weeks.

Mode of delivery was purely decided upon obstetric indications. All patients were carefully monitored throughout labour with intermittent auscultation and electro tonic monitoring. Eighteen cases in group A while twenty two cases in group B underwent caesarean section (p value= ns).

Regarding the perinatal outcome no significant difference was observed in the outcome of both the groups. Twenty six cases (86.7%) in group A and 25 cases (83.3%) in group B attained live births (p value= ns).The rate of preterm birth 34 to 37 weeks was 8(26.7%) in group A and 6(20%) in group B (*p value*= ns). Mean birth weight difference was also not statistically significant. It was recorded as 3.0 ± .135 in group A and 3.1±.114 in group B (p value =ns).

Regarding assessment for common side-effects of Aspirin and Heparin, bruising and injection site pain was significantly high for group B (p value<.001).Bruising was noted in 50% (15) cases and injection site pain was complained by 73% (22) cases (Table III).

Table III. Comparison of Side effects between both the groups

Side-Effects	Aspirin alone	Heparin + Aspirin	p value
Bruising	0 (0%)	15 (50%)	< 0.001
Injection site pain	0 (0%)	22 (73.3%)	< 0.001
Thrombocytopenia	1 (3.3%)	2 (6.7%)	0.554
Heart burn	9 (30%)	11 (36.7%)	0.584
Reaction	0 (0%)	1 (3.3%)	0.313
Cost	Rs 300	Rs 6300	< 0.001

Estimated cost of drug use over 28 weeks was again significantly high for group B. As mentioned earlier It was Rs 300 only for group A and Rs 6300 for those using Heparin. Further more It was Rs 9300 for those using Clexene for group B (*p value*<.001).

Discussion

Recurrent pregnancy loss is a disease distinct from infertility defined by 2 or more failed pregnancies. Although approximately 25% of all recognized pregnancies end in miscarriages, less than 5% experience 2 miscarriages and only 1% experiences 3 or more miscarriages.[9] After 3 or more losses thorough evaluation is warranted.

Acquired and inherited thrombophilias are known to be associated with unfavourable pregnancy outcomes including recurrent fetal losses. When compared with controls, females with un-explained still births are more likely to be heterozygous for factor V lieden mutation, Protein C or S deficiency.[10]Although there is increased evidence of association between thrombophilia and fetal death there are no studies to guide management in the subsequent pregnancies. Blood tests for aCL and LA may identify women with acquired thrombophilia aPL, a cause for 3-15% recurrent miscarriages.[11]

On the basis of presumed similarities in pathogenesis between RMs associated with aPL and unexplained RMs. Aspirin and Heparin are frequently being prescribed for women with unexplained RPL. The basis of Heparin and low dose aspirin in improving fetal outcomes, comes from 3 studies[12-14] that compared aspirin/ Heparin with aspirin alone and reported benefit from the combined treatment. This combination may promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation.

Recently two randomized controlled trials have compared Heparin alone in the treatment for RPL. Fawzy clearly established benefit of Enoxaprin over placebo showing a live birth rate of 81% versus 48%, whereas Badawy compared use of Enoxaprin to no treatment and reported miscarriage rate of 5% and 11% respectively.[15,16]

Laskin et al[17] compared the LMWH (low molecular weight Heparin) with aspirin and aspirin alone in women with RPL (HepASA Trial) and found no difference in the outcome. It was a randomized controlled trial including patients with a history of RPL and at least one of the following i.e. aPL, an inherited thrombophilia or Antinuclear antibody being positive. The trial had to be stopped at 4 years when an interim analysis showed no difference in the live birth rate in the 2 groups (77.8% in the LMWH/ASA group and 79.1% in the ASA group- p value .71).

Kaandorp and colleagues[18] performed a systematic review to evaluate effectiveness and safety of Aspirin and Heparin in women with RPL without apparent causes other than inherited thrombophilia. Two studies were found eligible. Both studies included women with recurrent miscarriage but without detectable aCL antibodies. One RCT compared aspirin alone to placebo and found similar birth rates in both arms (81% with CI .78-1.29). The other RCT compared aspirin to enoxaparin and again found similar live birth rate with both the interventions (82% with aspirin, 84% with enoxaparin CI .81-1.16).

Though both Aspirin and Heparin are being widely prescribed in cases with RPL in our setup but yet there is paucity of local studies on the subject. A study conducted at Agha Khan University hospital, Karachi retrospectively analyzed the pregnancy outcome for women with recurrent miscarriages diagnosed with APS. Aspirin alone was used in 29 patients and in combination with Heparin in 35 patients. Analysis found no significant difference in fetal and

maternal complications including pregnancy induced hypertension, prematurity, IUGR and neonatal death between the two groups.[19]

Various other studies including randomized controlled trials and systematic reviews as above have been performed to assess the benefit of one treatment over the other, however limitations in methodology and difference in characteristics of study population and difference in interventions make it difficult to compare the results of these trials.

Most recent in this context is the ALIFE study (Anticoagulant therapy for living fetuses) which compared three anticoagulation strategies - aspirin alone, combined with Heparin and placebo.[20] In this trial Kaandorp and colleagues recruited 364 women with history of unexplained recurrent miscarriages and assigned them to three treatment arms. The live birth rate in the Heparin group was 69.1%, in the aspirin group it was 61.1% and in the placebo group it was 67%. It concluded that neither aspirin combined with heparin, nor aspirin alone improved the live birth rate as compared to placebo, among women with unexplained recurrent abortion.

It was a randomized controlled trial comparing aspirin alone with combination of aspirin with heparin. We addressed the confounding factors successfully at recruitment and found no significant difference in the perinatal outcome in both the groups. However the heparin group suffered significant bruising, pain and injection reaction. Furthermore there was exhaustive counselling and cost involved in the arm using additional Heparin and thus the results showing comparable outcome with Aspirin alone bears an important implications for a resource limited country like us.

Patients with 2 unexplained consecutive pregnancy losses prior to 32 weeks of gestation have an 80% chance of a subsequent live birth anyway.[21] In a much more closely defined group of women with diagnosed APS and three or more miscarriages the meta-analysis does show a common odds ratio of 2.63 in favour of Heparin (95% CI 1.46-4.75). But where there are un-explained recurrent losses without detection of aCL and LA these results cannot be applied. Future ideal trial will be to compare combined aspirin and heparin, aspirin alone to no treatment or placebo in cases with RPL. While further large RCT's are needed in this area, we must accept the fact that patients with RPL are bogged down with huge emotional burden and would grab every shred of hope. Choosing placebo or no treatment as compared to a treatment that offers even a glimmer of hope will definitely make recruitment for such trail a challenge.

Conclusion

RPL have comparable perinatal outcomes with LDA alone as compared to Heparin with LDA, with an added benefit of less pain and bruising, low cost and more convenience of administration. We therefore recommend that until further evidence is available the widespread use of Heparin in cases of recurrent pregnancy losses is not justified.

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What is Academic? When and where did this term start?

Plato (427-347BC) inventor of philosophy or follower of Socrates the truthful.

Plato gathered around him a group of people who persued philosophical discussions and teaching and enquired into mathematics and astronomy, which eventually gave rise to what we now call “Research”. The public space at the edge of Athens where Plato carried on his discussions was called the Academy and this is how plato gave the word of “Academic” to the world.

Ref: Bernard Williams. The invention of philosophy: In The great philosophers – from Socrates to Turing. Editors Ray Monk and Frederic Raphael. London: (Phoenix), GuernsyCl; 2000.p.47-66.

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