Selected Summaries

Pregnancy Termination for Growth Retardation—Is it Useful?

[Piper JM, Xenakis EM-J McFarland M, Elliott BD, Berkus MD, and hanger O. Do growth retarded preterm infants have different rates of perinatal morbidity than appropriately grown premature infants? Obstet Gynecol 1996, 87: 169-174].

Two common beliefs that growth retarded preterms have fewer complications of prematurity and that they may benefit from planned preterm delivery are questioned in this study.

Nondiabetic singleton pregnancies (24-36 weeks) who were sure of dates were an alyzed retrospectively. This resulted in a comparison of 1012 small for gestational age (SGA) infants with 3171 appropriate for gestational age (AGA) subjects over a 15 year period. SGA status was defined as birth weight less than 10th centile of the local population standards.

SGA pregnancies had a higher perinatal mortality rate (PNMR) than SGA (281 versus 170; OR 1.91 (95% CI 1.61-2.26). Both fetal death rate (168 versus 69; OR 2.74 (95% CI 2.2-3.41) and neonatal death rate (135 versus 108; OR 1.29 (95% CI 1.02-1.63) were higher in SGA infants as compared to the AGA group. Even after excluding congenital anomalies, trends of PNMR were similar.

Stratification by gestational age revealed a higher rate of PNMR and neonatal mortality rate (NMR) at all preterm gestations in SGA babies and a higher neonatal death rate compared to fetal death rate in SGA babies at all (24-36 weeks) gestational ages. Stratification by birth weight revealed no differences in mortality rates overall or in various categories. Comparison by gestational age categories revealed that hyaline membrane disease (HMD) incidence was higher in SGA babies in all preterm gestations (overall OR 1.70; 95% CI 1.29-2.23) compared with AGA peers. Comparison by birth weight categories revealed a lower incidence of HMD in SGA category (OR 0.75; 95% CI (0.58-0.95). The authors explained this finding on the fact that when stratified by birth weight, within each birth weight group, SGA babies had an advantage of being more mature by gestation. When stratified by gestation, the true effect of growth retardation was seen and thus both mortality risk and incidence of HMD were higher in SGA preterms than AGA preterms of the same gestation.

The authors concluded that: *(i)* growth retarded preterms have no survival advantage and growth retardation is an independent predictor of perinatal morbidity; *(ii)* SGA infants have higher PNMR, fetal death rate and neonatal death rate; and *(iii)* the increased risk of neonatal death outweights the risk of fetal death at all gestational ages and elective preterm delivery is not indicated for growth retardation.

Comments

Recognition of the fact that growth retardation is not protective forms the basisfor inclusion of SGA status (which is not synonymous with growth retardation, but commonly used interchangeably) in illness severity scoring system in sick neo-

nates (Score for Neonatal Acute Physiology-Perinatal Extension SNAP-PE). This score has been observed to correlate with the mortality risk, therapeutic intervention and length of stay in hospital(l).

The myth that stress accelerates lung maturity and HMD is rare in preterm SGA is not supported by the current study data on stratification by gestation groups. A higher HMD incidence and a higher incidence of respiratory distress in preterm SGA has also been shown in other series(2) including our own experience(3). Even full term SGA infants had more risk of respiratory distress than non SGA full term infants(4) a risk which was not explained by the higher cesarean rate and lower Apgar scores that these SGA infants have.

The conclusion of this study that growth retardation is not an indication for elective preterm delivery was primarily based on the finding of higher neonatal death rate in comparison total death rate at 24-36 weeks gestation. However, other important factors also need to be considered before arriving at such a conclusion. These include: *(a)* Cause and severity of growth retardation; *(b)* Acute on chronic events in intrauterine growth retardation (IVGR); (c) Cesarean section policy; and *(d)* Attitudes for neonatal care and quality of neonatal care over the years including the survival trends. Many perinatal teams deliver severely growth retarded babies beyond certain gestation (34-35 weeks) where the neonatal survival with the best possible care for outweighs the risk of fetal death. Such decisions are often individualized and vary across the Neonatal Intensive Care Units with time. Ideally, the risk of fetal death in each grade of IUGR in each disease at different gestational ages should be compared with neonatal survival rates in that particular set up.

The previous studies(5,6) which compared mortality at different gestations showed that the relationship between mortality and gestation in SGA was linear in one series(6) U shaped in another(5). Thus the optimal period of delivery of a severely retarded preterm may be less than 37 weeks if additional weight gain does not occur. If fetal growth retardation is severe conceivably mortality may be minimized by prompt delivery.

Hence, to summarize: (i) IUGR alone is not an indication for planned preterm delivery; and (ii) growth retarded fetuses need not be carried till term. If growth retardation is severe or other signs of compromise exist, these fetuses may be delivered beyond a certain "safe" gestational age derived by each individual perinatal unit.

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High-Dose Dexamethasone for Chronic/Refractory* Immune Thrombocytopenia

[Basto M), Lamas P, Cabrera R, Fernandez MN. Pulsed high-dose dexamethasone in the treatment of refractory immune thrombocyto-penia. Br J Haematol 1996, 93: 738-739].

Treatment of chronic idiopathic/immune thrombocytopenia (ITP) poses & challenge, particularly when the usually described therapeutic modalities fail to elicit the desired effect. In this brief communication the authors used pulsed high-dose dexamethasone (HDD) in some cases who were refractory to the earlier described methods of treatment. Three of the 5 cases of this series had ITP while one each had immune thrombocytopenia associated with severe combined immune deficiency and chronic lymphocytic leukemia. All were female patients between 14 to 69 years age. The median duration" of thrombocytopenia was 39 months (range 1 to 216 months). On an average, 3 prior treatments (range 1 to 6) had been received including conventional doses of corticosteroids. Two of the patients were splenectormised. Baseline platelet count was 15,000/mm^3 and bleeding symptoms were present in four of them.

Dexamethasone was given orally 40 mg once daily for 4 days every 28 days for 6 months. Three patients received complete 6 months course. Of these three patients, complete response (platelet count >l,20,000/mm^3) was seen after 1st or 2nd course in 2, while the third case had initial partial response (platelet count 50,000-120,000/mm^3). These three patients, till the time of reporting had sustained platelet count elevation for 4-6 months after stopping the therapy. The remaining 2 patients had no response to initial 2 courses and hence further therapy was discontinued. The drug as well tolerated, only minor side effects were observed. Authors concluded that HDD is an effective, well tolerated and relatively inexpensive method of treatment of chronic and refractory thrombocyto-penia.

Comments

Chronic ITP is a troublesome disease, both to the patient and to the treating physician. Various therapies have been tried and none is curative for all cases. Anderson (1) lists 14 therapeutic modalities used for he, who first used HDD in chronic ITP. All of his ten consecutive patients showed not only an initial response to this form of treatment but also had sustained elevation of platelet count (> 1 lac) for at least 6 months after the last course of HDD. Caulier et al.(2) did not get such good response in their series. Out of 10 cases, 1 had complete response and 4 had minor response. In 2 patients, complications necessitated stoppage of therapy while in remaining 3, it was a failure after 3-4 courses.

Anderson(l) had adopted this form of therapy from chemotherapy protocols of B

cell neoplasm which include dexamethasone for its lympholytic effect. In chronic ITP, it may destroy autoantibody producing B Cells(3). Anderson also took into consideration the tolerance, efficacy and pharmacokienetics of dexamethasone. Above all the cost of this mode of therapy was 10 to 3000 times less than other therapies(l).

All the three studies were done on small number of adults with certainity and the possibility of spontaneous remission can not be excluded with certainity. Before this therapy becomes an accepted form of treatment, larger trials including children and addressing comparison with placebo and other established forms of treatment like intravenous immunoglobulin or intravenous methyl-prednisolone are needed.

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Theophylline in Chronic Asthma

[Weinberger M, Hendeles L. Theophylline in asthma. N EngJ Med 1996, 334:1380-1388].

With the advent of many new medications for bronchial asthma especially inhaler therapy, the use of theophylline has declined considerably. The recent discovery of anti-inflammatory, immunomodulatory and bronchoprotective effects of this drug has stimulated further interest in its potential for treating chronic asthma.

The mechanisms of action of theophylline have not yet been clearly elucidated. It downregulates the function of inflammatory and immune cells, attenuates late phase increase in airway obstruction, decreases migration of eosinophils into the bronchial mucosa, decreases airway responsiveness to histamine, methacholine, allergen, sulfur dioxide and adenosine. At serum concentrations above 15 microgram per milliliter, it completely inhibits airway responsiveness to exercise. By directly inhibiting smooth muscle contraction it prevents bronchoconstriction by histamine and by decreasing release of leukotrienes and blockade of adenosine induced enhancement of mediator release from mast cells prevents bronchospasm due to exercise and allergens. All the above mentioned actions are unlikely to be useful in acute asthma. By decreasing fatigue in diaphragmatic muscles, increasing mucociliary clearance, acting centrally to block the decrease in ventilation that occurs with sustained hypoxia, theophylline is useful in the management of acute asthma with ventilatory failure. Inhibition of phosphodiesterase

types III and IV relaxes smooth muscles in airways whereas the anti-inflammatory or immunomodulatory actions result form inhibition of type IV isoenzymes.

In patients with acute asthma requiring hospitalization, role of theophylline is controversial. In controlled clinical trials in children with acute asthma addition of theophylline to inhaled albuterol and systemic steroids was not helpful(l). However, patients with respiratory failure were ot included in the study. Use of theophylline in patients with respiratory failure may be justified because of its central action and ability to decrease fatigue in diaphragmatic muscles. Although a therapeutic trial of theophylline may be helpful in selected patients of acute asthma with inadequate responses to inhaled beta agonists and systemic corticosteroid therapy, it is predominantly as maintenance therapy for chronic asthma that theophylline deserves special consideration. Its superior efficacy when compared with chromolyn, oral metaproterenol, oral slow release terbutaline and inhaled albuterol have been demonstrated in various controlled clinical trials(2-5). Though salmeterol has proved superior to theophylline, the loss of bronchoprotective effect with salmeterol after two weeks of use raises concern regarding its long term usefulness in chronic asthma(6). When compared to inhaled beclomethasone it was shown to be less efficacious but growth in theophylline treated children was more during the period of observation(7). Further, theophylline adds substantial clinical benefit to a regimen consisting of inhaled corticosteroid or oral prednisolone.

Three indications can currently be identified in chronic asthma for which theophylline provides a useful alternative to other available medications: primary therapy in cases in which the administration of an inhaled corticosteroid is difficult or cumbersome as in toddlers and preschool children, primary therapy in any patient judged more likely to adhere to a regimen of oral medication than an inhaled regimen, and additive therapy for patients whose asthma is not adequately controlled with conventional doses of an inhaled corticosteroid. Although the anti-inflammatory and immunomodulatory effects of theophylline are useful for preventive therapy, it is the ease of oral medication with sustained release theophylline are useful for preventive therapy, it is the theophylline that provide justification for its use. Inhaled corticosteroids are convenient, safe and effective for many patients. Although these can be administered to young uncooperative children by means of a holding chamber with a flexible tight fitting mask, daily therapy can be a trying experience for parents and success in the delivery of medication will vary. Use of sustained release theophylline in such patients proves beneficial. Despite the considerable potential benefit of theophylline, its narrow therapeutic index requires skill and knowledge on the part of the physician for safe and effective use of the drug.

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