Prevention of Intracranial Hemorrhage

Henrietta S. Bada, MD*

OBJECTIVES

After completing this article, readers should be able to:

1. **Explain how delaying or preventing preterm delivery can reduce the risk of intracranial hemorrhage (ICH).**
2. **Explain how the use of forceps during vaginal delivery may protect against ICH.**
3. **List the postnatal factors that may influence the risk of developing ICH.**
4. **Delineate supportive measures after birth that can minimize the risk of ICH.**

Introduction

Intracranial hemorrhage (ICH) is a major neurologic complication in preterm infants. Its incidence is inversely related to gestational age or birthweight. Because of its multifactorial etiopathogenesis, the "silver bullet" that will prevent ICH still does not exist. However, numerous studies have addressed various modalities for prevention of this event in both antenatal and postnatal periods.

The increased risk of ICH among preterm infants may be explained by the preterm infant's brain structure. The major feature of the immature brain is the presence or prominence of the periventricular germinal matrix, a highly vascularized structure. The germinal matrix contains capillaries with a low blood flow. Abrupt or severe changes in blood flow can disrupt endothelium and cause ICH into the tissues of the periventricular germinal matrix. Because of this unique brain morphology in preterm infants, obstetric strategies for prevention of ICH are aimed at preventing preterm deliveries.

ICH is identified in more than 90% of cases by 4 to 5 days of age, but 30% to 50% of these hemorrhages are present within 12 hours of age, and it has been estimated that 40% occur as early as 1 hour of age. Preventive measures would differ for early-onset versus later-onset ICH. Antenatal measures are likely to affect early ICH, and postnatal measures probably will influence later-onset ICH. Because early-onset ICH is more likely to evolve in severity, its prevention can result in an overall decreased incidence of severe ICH.

Departments of Pediatrics and Obstetrics and Gynecology, The University of Tennessee, Memphis, TN.

Antenatal Prevention Strategies

Antenatal strategies range from prevention of preterm birth and careful fetal surveillance to various delivery options and administration of pharmacologic agents (Table 1).

PREVENTION OF PRETERM DELIVERY

Administration of tocolytics has been the mainstay in the management of preterm labor, with the primary goal of preventing preterm delivery. Studies indicate that the use of tocolytics has been associated with a reduced incidence of ICH. Successful prevention or a delay of preterm delivery reduces the risk of respiratory distress syndrome, which is a known risk factor for development of ICH. Tocolytic agents include magnesium sulfate, beta-sympathomimetics, and indomethacin.

Indomethacin inhibits the synthesis of prostaglandins, substances that play a role in the initiation and progression of labor. Although some studies indicate that postnatal administration of indomethacin may be associated with a reduced incidence of ICH, its antenatal use as a tocolytic has been associated with neonatal complications. Of concern are conditions that probably are the result of the drug's vasoconstrictive effects in the fetus or the neonate, such as renal insufficiency, pulmonary hypertension, in utero closure of the patent ductus arteriosus, periventricular leukomalacia, and ileal perforation.

OTHER ANTENATAL MEASURES

Optimal fetal surveillance and the emergent treatment of fetal distress as soon as the situation is identified will ensure delivery of a preterm infant in optimal condition. In addition to intrapartum fetal distress, acidosis and vaginal bleeding are some factors that have been reported to be associated with severe hemorrhages or hemorrhage that extends into the parenchyma. Thus, antenatal management should be directed toward treatment of these risk factors.

ACTIVE PHASE LABOR AND MODE OF DELIVERY

Much has been written about the role of labor and mode of delivery on the development of ICH. Reports suggest a higher incidence of early ICH with active phase labor and vaginal delivery. However, this negative effect is attenuated by application of outlet forceps. Uterine contractions affect placental gas exchange, and active labor may aggravate an already compromised fetal oxygenation that results from conditions that may have triggered preterm labor. The use of forceps during vaginal deliveries allows for a slow transition as the counterpressure to the fetal head abruptly decreases when the head descends from the vaginal canal. Forceps application also may allow a well-controlled delivery process. Cesarean section with latent phase or no labor appeared to protect against early ICH compared with vaginal deliveries without forceps. However, even in the absence of active labor, cesarean section has not been shown to afford protection against late ICH.

TABLE 1. Antenatal Strategies for Prevention of ICH

- Prevention of preterm delivery
  - — Tocolytics (beta sympathomimetics, magnesium sulfate, indomethacin)
- Treatment of maternal complications (bleeding, chorioamnionitis, toxemia, hypertension)
- Intrapartum fetal surveillance
  - — Biophysical monitoring
  - — Prompt delivery upon recognition of fetal compromise
- Obstetric interventions (mode of delivery/labor)
  - — Controlled vaginal delivery
  - — Outlet forceps
  - — Cesarean section
  - — Anesthesia
- Pharmacologic agents
  - — Vitamin K–uncertain or no benefit
  - — Phenobarbital–uncertain or no benefit
  - — Steroids–benefit related to decreased incidence and severity of respiratory distress syndrome

TYPE OF ANESTHESIA AND RISK OF ICH

When performing delivery by cesarean section, the choice of anesthesia may influence the risk of intraventricular hemorrhage. In one investigation of infants delivered by cesarean section, a higher proportion of those delivered with general anesthesia had an Apgar score at 1 minute of 3 or less, respiratory distress syndrome, patent ductus arteriosus, and intraventricular hemorrhage compared with those delivered to mothers who received epidural anesthesia. Intervillous blood flow is maintained with administration of epidural anesthesia compared with a significant reduction in intervillous blood flow after induction with general anesthesia. The fetoplacental circulation remains unchanged with epidural anesthesia, as demonstrated by Doppler ultrasonography.

PHARMACOLOGIC AGENTS

A randomized trial of antenatal administration of vitamin K at an estimated gestational age of less than 32 weeks showed a reduction of ICH from 36% to 16%. The treatment significantly improved neonatal prothrombin time, and there was a trend toward improved partial thromboplastin time. There is a question, however, whether maternal vitamin K administration actually improves the infant's coagulation status. Although preterm infants have reduced vitamin K-dependent coagulation activity compared with term infants, this is believed to be a result of reduced synthesis of hepatic coagulation precursor proteins rather than vitamin K deficiency. Measurement of multiple coagulation factors would be needed to establish the effect of vitamin K in prevention of ICH.

The mechanism by which phenobarbital could influence the risk of ICH may be related to its effects on cerebral hemodynamics, metabolic rate, and catecholamine release and its scavenging activity against oxygen radicals. Phenobarbital lowers cerebral blood flow during acute hypertensive episodes and when hypoxia occurs during hypertension. It has been shown to have a neuroprotective effect as a scavenger of oxygen radicals by protecting against damage to the membranes of endothelial cells by oxygen free radicals. Earlier studies with small sample sizes demonstrated a decreased incidence of grades 3 to 4 ICH or severe hemorrhage following antenatal phenobarbital administration. However, a recent multicenter, prospective, randomized trial conducted through the NICHD Neonatal Research Network showed no protective effect from the administration of antenatal phenobarbital. Phenobarbital was administered at an initial dose of 10 mg/kg intravenously over 20 to 40 minutes, and saline was administered in the placebo group. Oral maintenance doses of 100 mg of phenobarbital (or placebo) were given daily. The proportion of ICH or deaths within the first 72 hours of life was similar between the phenobarbital- and placebo-treated groups. When infants younger than 34 weeks of gestation were examined, a similar percentage (23%) developed ICH in the both treatment groups. No adverse effects were detected in the infants as a result of maternal phenobarbital administration. More women in the phenobarbital-treated group became very sedated after intravenous administration of the drug compared with the placebo group (23% versus 5%).

The use of antenatal corticosteroids has increased as a result of a consensus conference sponsored by the National Institutes of Health, National Institute of Child Health and Human Development regarding their use in the prevention of respiratory distress syndrome in preterm infants. The maturational effects of steroids on the developing lung help to prevent respiratory distress syndrome, which can lower the risk of ICH. However, Leviton et al (see Suggested Reading) found that the protective effect of antenatal corticosteroids on the development of ICH did not change significantly when controlling for factors indicating enhancement of lung maturation. Corticosteroids may play a role in promoting maturation of the germinal matrix vessels. Studies also have shown that corticosteroids influence the blood-brain barrier, cell proliferation and differentiation, and neurotransmitter regulation. Corticosteroid administration results in maturation of the catecholamine response and myocardial adenyl cyclase activity, which can promote a stable blood pressure and decrease the need for volume expansion. Furthermore, antenatal steroids administered in conjunction with tocolytics or after preterm rupture of membranes have been shown to decrease the risks of grades 3 to 4 ICH. The incidence of early ICH was decreased further when antenatal steroids were used in conjunction with cesarean section delivery. Of some concern is the reported increase in maternal and neonatal infection when antenatal steroids are administered in the presence of preterm rupture of membranes.

It is not established whether antenatal betamethasone is superior to dexamethasone. It also is not clear whether there is any advantage to

administering more than a single course of steroids. Banks and colleagues (see Suggested Reading) recently reported that three or more courses of antenatal corticosteroids were associated with increased mortality (odds ratio of 2.8, 95% confidence interval of 1.3 to 5.9), decreased fetal growth, and fetal adrenal suppression.

Postnatal Prevention/Interventions

Postnatal measures are directed primarily at preventing neonatal factors that are associated with an increased risk of hemorrhages (Table 2). The effects of these strategies can be enhanced by an optimal neonatal state at the time of birth. Postnatal factors that may influence the risk of developing ICH include acidosis, hypoxemia, hypercarbia, the need for resuscitation, respiratory distress syndrome, pneumothorax and other air leak syndromes, and mechanical ventilation.

TABLE 2. Postnatal Preventive Measures

- Supportive measures
  - — Resuscitative measures as indicated
  - — Maintenance of adequate oxygenation, ventilation, and acid-base balance
  - — Mechanical ventilator settings at minimal to prevent pneumothorax and other air leaks and to minimize circulatory disturbance
  - — Minimization of abrupt hemodynamic alterations
    - Stabilization of blood pressure
    - Minimal handling to prevent hypertensive spikes
    - Slow volume infusion to treat hypotension
    - Inotropic agents/pressors to maintain stable, normal-range blood pressure and circulation
  - — Careful administration of surfactant while carefully monitoring associated systemic hemodynamic changes
- Pharmacologic agents of uncertain benefit
  - — Pancuronium
  - — Ethamsylate
  - — Phenobarbital
  - — Vitamin E
  - — Indomethacin

Also reported to be associated with an increased risk for ICH are conditions associated with cerebral hemodynamic alterations. Such alterations are observed when there is a large left-to-right shunt at the level of the patent ductus arteriosus, resulting in blood flow being siphoned from the cerebral arteries, or following ligation or closure of the ductus arteriosus, which can result in an abrupt increase in cerebral blood flow. Hemodynamic derangements also occur during hypotension, hypertensive spikes, rapid volume expansion, or when there is wide coefficient of variation in arterial blood pressure and in cerebral blood flow velocity (ie, simultaneous fluctuating patterns of arterial blood pressure and cerebral blood flow velocity). The increased likelihood of a preterm infant developing alterations in cerebral circulation in these situations is explained by impairment of cerebral blood flow autoregulation (ie, when cerebral flow becomes pressure-passive).

Other postnatal conditions that may influence the risk of developing ICH include coagulation/platelet disorders and the generation of oxygen radicals and prostaglandins, substances that mediate hemodynamic changes and cellular injury. The postnatal prevention of ICH involves a multiple systems approach and should be directed toward maintaining a stable biochemical, hemodynamic, metabolic, and hematologic milieu for the infant.

SUPPORTIVE MEASURES

Important preventive and supportive measures that may need to be instituted soon after birth include maintenance of oxygenation, adequate ventilation, and optimum acid-base status. This can be achieved by vigilantly monitoring the infant's blood gases and pH and promptly instituting corrective measures, such as adjusting Fio_2 as indicated, changing ventilator settings (peak inspiratory pressure, positive end expiratory pressure, inspiratory time, ventilator rate), and when necessary, administering a buffer. Ventilatory support should be provided at the most minimal settings to prevent complications such as pneumothorax, other air leaks, or deleterious effects of peak inspiratory pressure and mean airway pressure on the cerebral circulation.

In conjunction with monitoring for hemodynamic derangements, certain measures may be instituted to minimize the risk of ICH. These interventions include maintaining the stability of the blood pressure, expanding volume slowly, and minimizing increases in blood pressure or hypertensive spikes through minimal handling when providing neonatal intensive care. Inotropic agents may be needed if there is myocardial dysfunction and consequent hypotension.

If preterm delivery cannot be prevented, antenatal preventive measures cannot be instituted, and an infant develops respiratory distress syndrome, surfactant is administered to treat surfactant deficiency. Studies have demonstrated improvement of respiratory status following administration of surfactant, which subsequently reduces the risk of ICH. Published data from some studies of surfactant as a rescue treatment have suggested an increase in ICH among very low-birthweight infants, but this is not a consistent finding. The risk of ICH attributable to surfactant has been suggested to be due to the associated hemodynamic changes that occur with the intratracheal route of administration. The risk may be minimized by careful intratracheal instillation of surfactant and slowly changing the infant's position with each aliquot of drug administered, thereby reducing alterations in hemodynamics.

PHARMACOLOGIC PREVENTION

Infants who have severe respiratory distress may demonstrate fluctuating arterial blood pressure and cerebral blood flow velocity. Studies by Perlman et al (see Suggested Reading) showed that the use of muscle

paralysis induced by administration of pancuronium reversed both blood pressure and the cerebral blood flow velocity pattern to normal and significantly lowered the incidence of ICH. The effect of muscle paralysis on ICH prevention is attributed to simultaneous stabilization of arterial blood pressure and cerebral blood flow.

Ethamsylate is a nonsteroidal, water-soluble drug that has been approved for use in Europe to prevent or reduce capillary bleeding during surgical procedures. Prostacyclin inhibition with a resulting decrease in cerebral vasodilation probably is the underlying mechanism for its preventive effect in ICH. Ethamsylate also promotes platelet adhesiveness and polymerizes capillary basement membrane. Two clinical trials suggested that administration of the drug soon after birth might reduce the risk of ICH. Another multicenter trial (The European Community Ethamsylate Trial Group) recruited 334 preterm infants at gestational ages of 32 weeks or younger within 4 hours of birth and randomized them to receive ethamsylate or no ethamsylate. The incidence of ICH in the ethamsylate group was 35%, which was not significantly different from the 37% incidence in the control group. There were no differences between groups in morbidity. Further data on long-term morbidity relating to ethamsylate administration are still lacking. This trial provided little evidence to support the use of ethamsylate for routine prophylaxis.

Several studies have examined the postnatal use of phenobarbital to prevent ICH. The mechanism for its effect is attenuation of increases in cerebral blood flow associated with motor activity, procedures, or handling as part of the delivery of neonatal intensive care. Phenobarbital also may protect against free radical injury due to reperfusion or reoxygenation following ischemia or hypoxemia. Results from preventive studies are conflicting. Most studies did not document a reduction in the incidence or severity of ICH. In one randomized, placebo-controlled study, phenobarbital administered initially at no more than 12 hours of age was associated with an increased risk of developing any grade of hemorrhage. The increased risk was apparent even when controlling for confounders.

The beneficial effects of vitamin E administration are likely due to its antioxidant properties. Vitamin E acts as a scavenger of free radicals, thereby protecting the vascular endothelial cells from injury that may occur with reperfusion following episodes of hypoxia-ischemia. Results of one investigation of intramuscular administration of vitamin E to infants whose birthweights were 1,000 g or less documented a decrease in ICH in a subgroup whose birthweights were 500 to 750 g (29% versus 60% in control infants). Severe hemorrhage occurred in 4% of these infants compared with 32% of controls. One concern about this study was the high rate and marked severity of ICH in the control group. Enthusiasm for this therapeutic approach has been tempered by the report of a high incidence of ICH among infants receiving vitamin E for prevention of retinopathy of prematurity.

Indomethacin is a prostaglandin H synthase inhibitor. Its administration results in decreased production of dilator prostaglandins, which have been shown to be elevated among infants who suffer respiratory distress. By inhibiting prostacyclin receptor-mediated vasodilation, indomethacin can cause vascular constriction and a decrease in organ blood flow. Restoration of blood flow to baseline levels occurs hours after its administration. Indomethacin also attenuates the hyperemic response to hypoxia, hypercapnia, and hypertension and stabilizes cerebral blood flow at the upper limits of autoregulation. Finally, indomethacin inhibits generation of oxygen free radicals and promotes maturation of germinal matrix microvessels. Meta-analysis of studies of indomethacin for ICH prevention indicates a lower incidence of ICH, especially the severe (grades 3 to 4) hemorrhages. However, these studies varied in drug dosage, interval of administration, and postnatal age of infants at the initiation of prophylaxis.

The collaborative randomized trial by Ment and colleagues (see Suggested Reading) documented a significant reduction in the incidence of ICH with low-dose indomethacin (0.1 mg/kg per day every 24 h x 3 d). Developmental follow-up of the cohort showed no increased incidence of cerebral palsy in those who received indomethacin prophylaxis, and intelligence quotient scores of the children were related to ICH, birthweight, and maternal education. However, a recent report suggests an increased risk of necrotizing enterocolitis and chronic lung disease among babies whose birthweights were 1,000 g or less at neonatal centers routinely employing early low-dose indomethacin prophylaxis. Because the significant vasoconstrictive effect of this drug leads to decreased organ blood flow, it must be administered cautiously during episodes of hypoxia, hypercapnia, acidosis, hypothermia, or hypotension. The decrease in blood flow following its administration may become exaggerated. Indomethacin should be infused slowly, over no less than 30 minutes. A large multicenter trial currently is underway in neonatal intensive care units in Canada and the United States to determine the efficacy of routine indomethacin prophylaxis.

Conclusion

Many reasonable clinical practices can decrease the risk of ICH in preterm infants. These include treatment of preterm labor, antenatal administration of corticosteroids to enhance lung maturity, intrapartum fetal surveillance, prompt delivery upon diagnosis of fetal distress, resuscitation of the depressed infant at delivery, and postnatal supportive measures to maintain optimal physiologic, biochemical, metabolic, and hematologic states. However, clinicians should remain cautious about routine administration of pharmacologic agents antenatally or postnatally for ICH prevention.

SUGGESTED READING

Abdel-Rahman AM, Rosenberg AA. Prevention of intraventricular hemorrhage in the premature infant. *Clin Perinatol.* 1994;21: 505–521

Bada HS. Routine indomethacin prophylaxis:

has the time come? *Pediatrics.* 1996;98: 784–785
Ballard RA, Ballard PL. Antenatal hormone therapy for improving the outcome of the preterm infant. *J Perinatol.* 1996;16: 390–396
Banks BA, Canaan A, Morgan MA, et al. Multiple courses of antenatal corticosteroids and outcome of premature neonates. *Am J Obstet Gynecol.* 1999;181:709–717
Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. *J Pediatr.* 1996;128:601–605
Egerman RS, Mercer BM, Doss JL, Sibai BM. A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. *Am J Obstet Gynecol.* 1998; 179:1120–1123
Elimian A, Verma U, Canterino J, Shah J, Visintainer P, Tejani N. Effectiveness of antenatal steroids in obstetric subgroups. *Obstet Gynecol.* 1999;93:174–179
Ethamsylate Trial Group. The EC randomised controlled trial of prophylactic ethamsylate for very preterm neonates. Early mortality and morbidity. *Arch Dis Child.* 1994;70: F201–F205
Fish WH, Cohen M, Franzek D, Williams JM, Lemons JA. Effect of intramuscular vitamin E on mortality and intracranial hemorrhage in neonates of 1000 grams or less. *Pediatrics.* 1990;85:578–584
Fowlie PW. Prophylactic indomethacin: systematic review and meta-analysis. *Arch Dis Child.* 1996;74:F81–F87
Gunkel JH, Banks PLC. Surfactant therapy and intracranial hemorrhage: review of the literature and results of new analyses. *Pediatrics.* 1993;92:775–786
Horbar JD. Prevention of periventricular-intraventricular hemorrhage. In: Sinclair JC, Bracken MD, eds. *Effective Care of the Newborn Infant.* Oxford, England: Oxford University Press; 1992:562–589
Kuban KCK, Leviton A, Krishnamoorthy KS, et al. Neonatal intracranial hemorrhage and phenobarbital. *Pediatrics.* 1996;77: 443–450
Leviton A, Kuban KC, Pagano M, Allred EN, Van Marter L. Antenatal corticosteroids appear to reduce the risk of postnatal germinal matrix hemorrhage in intubated low birth weight newborns. *Pediatrics.* 1993; 91:1083–1088
Ment LR, Oh W, Ehrenkranz RA, Philip AGS, Duncan CC, Makuch RW. Antenatal steroids, delivery mode, and intraventricular hemorrhage in preterm infants. *Am J Obstet Gynecol.* 1995;172:795–800
Ment LR, Vohr B, Oh W, et al. Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the multicenter indomethacin intraventricular hemorrhage prevention trial. *Pediatrics.* 1996;98: 714–718
Merrill JD, Clyman RI, Norton ME. Indomethacin as a tocolytic agent: the controversy continues. *J Pediatr.* 1994;124: 734–736
Morales WJ, Angel JL, O'Brien WF, Knuppel RA, Marsalisi F. The use of antenatal vitamin K in the prevention of early neonatal intraventricular hemorrhage. *Am J Obstet Gynecol.* 1988;159:774–779
Palta M, Sadek M, Lim T-S, Evans M, McGuinness G. Association of tocolytic therapy with antenatal steroid administration and infant outcomes. *Am J Perinatol.* 1998;15:87–92
Paneth N, Pinto-Martin J, Gardiner J, et al. Incidence and timing of germinal matrix/intraventricular hemorrhage in low birth weight infants. *Am J Epidemiol.* 1993;137: 1167–1176
Perlman JM. Antenatal glucocorticoid, magnesium exposure, and the prevention of brain injury of prematurity. *Sem Pediatr Neurol.* 1998;5:202–210
Perlman JM. White matter injury in the preterm infant: an important determination of abnormal neurodevelopment outcome. *Early Hum Dev.* 1998;53:99–120
Phelps DL, Rosenbaum AL, Isenberg SJ, Leake RD, Dorey FJ. Tocopherol efficacy and safety for preventing retinopathy of prematurity: a randomized, controlled, double-masked trial. *Pediatrics.* 1987;79: 489–500
Pomerance JJ, Teal JG, Gogolok JF, Brown S, Stewart ME. Maternally administered antenatal vitamin K_1: effect on neonatal prothrombin activity, partial thromboplastin time, and intraventricular hemorrhage. *Obstet Gynecol.* 1987;70:235–241
Rolbin SH, Cohen MM, Levinton CM, Kelly EN, Farine D. The premature infant: anesthesia for cesarean delivery. *Anesth Analg.* 1994;78:912–917
Shankaran S, Papile LA, Wright LL, et al. The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. *N Engl J Med.* 1997;337: 466–471
Shaver DC, Bada HS, Korones SB, Anderson GD, Wong SP, Arheart KL. Early and late intraventricular hemorrhage: the role of obstetric factors. *Obstet Gynecol.* 1992;80: 831–837
Sinha S, Davies J, Toner N, Bogle S, Chiswick M. Vitamin E supplementation reduces frequency of periventricular haemorrhage in very preterm babies. *Lancet.* 1987;1:466–471
Thorp JA, Parriott J, Ferrette-Smith D, Meyer BA, Cohen GR, Johnson J. Antepartum vitamin K and phenobarbital for preventing intraventricular hemorrhage in the premature newborn: a randomized double-blind, placebo-controlled trial. *Obstet Gynecol.* 1994;83:70–76
Vohr B, Ment LR. Intraventricular hemorrhage in the preterm infant. *Early Hum Dev.* 1996;44:1–16
Yang Y-M, Simon N, Maertens P, Brigham S, Liu P. Maternal-fetal transport of vitamin K_1 and its effect on coagulation in premature infants. *J Pediatr.* 1989;115: 1009–1013

NEOREVIEWS QUIZ

Quiz also available online at www.neoreviews.org.

4. Among the following, the mode of delivery associated with the *lowest* risk of early-phase intracranial hemorrhage (ICH) is:
   A. Active phase labor.
   B. Cesarean section no labor.
   C. Induced labor.
   D. Vaginal delivery without forceps.

5. Postnatal supportive measures that may reduce the risk of ICH include all of the following *except*:
   A. Administering inotropic agents if cardiac dysfunction results in hypertension.
   B. Expanding volume slowly.
   C. Maintaining a stable blood pressure.
   D. Maintaining ventilatory support at maximal levels.
   E. Monitoring blood gases and pH.

6. Because of its mechanism of action, indomethacin should be administered cautiously to preterm infants who have a:
   A. Blood pH of 7.27.
   B. Bilirubin of 5 mg/dL.
   C. Mean arterial pressure of 30 torr.
   D. $Paco_2$ of 45 torr.
   E. Pao_2 of 35 torr.

Prevention of Intracranial Hemorrhage

Henrietta S. Bada

NeoReviews 2000;1;e48
DOI: 10.1542/neo.1-3-e48

Prevention of Intracranial Hemorrhage

Henrietta S. Bada

NeoReviews 2000;1;e48
DOI: 10.1542/neo.1-3-e48