ARTICLE

Neurodevelopmental Follow-up at 36 Months' Corrected Age of Preterm Infants Treated With Prophylactic Indomethacin

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Background: Previous reports have suggested that prophylactic indomethacin decreases cerebral blood flow and may play a role in the development of ischemic brain injury and developmental handicaps.

Objective: To assess the neurodevelopmental outcome of subjects at 36 months' corrected age (CA) who, as low-birth-weight infants, received prophylactic low-dose indomethacin within the first 24 hours of life to prevent patent ductus arteriosus.

Setting: Newborn intensive care nursery and outpatient follow-up clinic at Children's Hospitals and Clinics of Minneapolis, Minneapolis, Minn.

Design: Ninety infants with birth weights of 600 to 1250 g were entered into a prospective, randomized, controlled trial to receive either prophylactic indomethacin, 0.1 mg/kg, or placebo in the first 24 hours and again every 24 hours for 6 doses to prevent patent ductus arteriosus. Nonresponders were treated with standard therapeutic indomethacin or ligation. Neurodevelopmental assessment at approximately 36 months' CA included medical and developmental histories, physical examinations, and developmental testing using the Bayley II Scales of Infant Development on subjects up to 42 months' CA. Subjects were classified as (1) normal, (2) mildly to moderately abnormal, or (3) severely impaired.

Results: Forty-two (98%) of 43 subjects who received prophylactic indomethacin survived compared with 46 (98%) of 47 who received placebo. Sixty-six (75%) of 88 survivors were seen for neurodevelopmental assessment at 36 months' CA. This group included 29 (69%) of 42 who received prophylactic indomethacin and 37 (80%) of 46 who received placebo. Twenty-three (79%) of 29 infants in the prophylactic indomethacin group had normal neurodevelopmental assessments at 36 months' CA compared with 26 (70%) of 37 placebo-treated subjects ($P = .68$). Of 4 significantly impaired subjects treated with prophylactic indomethacin, 1 had spastic diplegia; 1, spastic quadriplegia; 1, cognitive delay; and 1, significant motor delay. Of 8 significantly impaired placebo-treated subjects, 7 had spastic diplegia; 1, microcephaly.

Conclusion: The use of prophylactic low-dose indomethacin when initiated in the first 24 hours of life in low-birth-weight infants to prevent patent ductus arteriosus is not associated with adverse neurodevelopmental outcome at 36 months' CA.

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SINCE THE MID 1970s, it has been recognized that considerable left-to-right shunting through the patent ductus arteriosus (PDA) in premature infants with hyaline membrane disease (HMD) contributes to increased morbidity and mortality rates.[1,2] Infants with HMD who receive surfactant treatment have a more rapid decrease in pulmonary vascular resistance and are more susceptible to developing a hemodynamically notable PDA than similar infants not receiving surfactant.[3] Extremely premature infants who receive prophylactic surfactant in the delivery room are at the greatest risk for PDA. The prophylactic use of indomethacin for the prevention of PDA has been shown to reduce the incidence of symptomatic PDA, the need for surgical ligation, and the occurrence of pulmonary hemorrhage.[4,5] In addition, prophylactic indomethacin, when initiated within 24 hours following birth, has been shown to significantly decrease severe (grade 3 and grade 4) intraventricular hemorrhage (IVH).[6]

Previously, we reported that a course of prophylactic low-dose indomethacin therapy, when initiated within 24 hours of birth, decreased ductal shunting in a randomized, prospective, controlled trial involving 90 infants with birth weights between 600 to 1250 g who received prophylactic surfactant in the delivery room.[4] However, the long-term effects of prophy-

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PATIENTS AND METHODS

PATIENTS

Between June 3, 1995, and October 18, 1995, 90 infants with birth weights between 600 and 1250 g and gestational ages between 23 and 29 weeks were enrolled in a prospective, randomized, blinded study to test the hypothesis that a course of prophylactic low-dose indomethacin, when initiated within the first 24 hours of life, would decrease the incidence of PDA in preterm infants who received prophylactic surfactant in the delivery room. These infants were admitted to the newborn intensive care unit (NICU) at Children's Hospitals and Clinics of Minneapolis, Minneapolis, Minn. All but 1 of these infants were inborn. Gestational age was estimated by obstetrical dates and confirmed by prenatal ultrasonography or findings from newborn examination. All infants underwent immediate tracheal intubation and stabilization following birth and received prophylactic surfactant (Survanta; Ross Laboratories, Columbus, Ohio) in the delivery room within 5 minutes of birth. Surfactant was administered intratracheally according to the manufacturer's directions, and infants were eligible to receive additional surfactant treatment during their hospitalization at the discretion of the attending neonatologist. All infants at study entry received mechanical ventilation via an orotracheal tube by means of time-cycled, pressure-limited ventilators. Ventilator settings were adjusted to maintain arterial oxygen tension between 50 and 80 mm Hg, arterial carbon dioxide tension between 35 and 50 mm Hg, and a pH value between 7.28 and 7.45. The diagnosis of HMD required pertinent chest radiographic findings. The diagnosis of sepsis required positive findings from blood culture. Bronchopulmonary dysplasia (BPD) was defined as the need for supplemental oxygen at 28 days of life, with abnormal findings on chest radiography. Infants at risk for BPD were treated with postnatal corticosteroids in a manner previously described by Avery et al.[11]

NICU PROTOCOL

After obtaining parental consent, each infant underwent an echocardiographic examination in the first 24 hours of life before randomization and treatment to assess the status of the PDA. Patients then underwent prospective, blinded, random assignment to receive either prophylactic indomethacin sodium trihydrate (Indocin; Merck, West Point, Penn), 1.0 mg/mL, for injection, or placebo (isotonic sodium chloride solution for injection) (LyphoMed Inc, Rosemont, Ill) as previously described. A follow-up echocardiographic study was performed on postnatal day 7, 24 hours after the last dose of prophylactic indomethacin, to reassess the status of the PDA. If a hemodynamically notable PDA was confirmed during study treatment, the infant was considered a study treatment nonresponder and was treated with either standard therapeutic indomethacin dosages[12] or surgical ligation at the discretion of the attending neonatologist.

Cranial ultrasounds were obtained on days 7 and 28 as part of the routine NICU protocol and were graded for IVH according to Papile et al.[13] Cranial ultrasounds were also assessed for parenchymal echodensities representing ischemic events. Echodense abnormalities that later showed cystic changes were classified as periventricular leukomalacia.[14]

NEURODEVELOPMENTAL FOLLOW-UP

Neurodevelopmental follow-up evaluation on all available infants included medical and developmental histories obtained by a nurse practitioner and physical examinations performed by a developmental neonatologist, an occupational therapist, and a pediatric ophthalmologist, and was performed between 30 and 42 months' CA depending on availability. Developmental testing included the Bayley II Scales of Infant Development for subjects up to 42 months' CA. Subjects were classified as normal if there were no serious abnormalities on physical and/or neurologic examination and if developmental testing scores on the Bayley II Scales of Infant Development were within 1 SD of the mean. Subjects were classified as mildly to moderately abnormal if they had at least 1 of the following disabilities: isolated muscle tone abnormalities (mild hypotonia or hypertonia), strabismus, unilateral blindness, hyperactivity, or if their developmental testing scores were between 1 and 2 SDs below the mean. Subjects were classified as severely impaired if they had at least 1 of the following disabilities: blindness, spasticity, deafness, hydrocephalus, or severe delay or if their developmental testing scores were more than 2 SDs below the mean. Diagnosis of cerebral palsy, including diplegia, quadriplegia, and hemiplegia, was based on the presence of hypertonicity, hyperreflexia, and dystonic or spastic movement in the involved extremities. All neurodevelopmental assessments were done by individuals blinded to previous assignment of the infants to either the prophylactic indomethacin or placebo groups.

The study protocol was approved by the Institutional Review Board for Approval of Research Involving Human Subjects at Children's Hospitals and Clinics of Minneapolis. Informed parental consent was obtained for all enrolled patients.

STATISTICAL ANALYSIS

The differences between the prophylactic indomethacin and placebo groups were analyzed for statistical significance by means of the unpaired t test and χ^2 analysis. In addition, ordered logistic regression using commercial statistical software (SAS/STAT software; SAS Institute Inc, Cary, NC) was carried out in which the outcome variable was neurologic status at 3 years' CA, with normal status coded as 1; mild to moderate abnormality, 2; and severe impairment, 3. Drug group was entered into the model as an indicator variable for prophylactic indomethacin use (1, prophylactic indomethacin; 0, placebo). A number of analyses were carried out to analyze for the effects of prophylactic indomethacin after controlling for other variables that might have a plausible relationship to neurologic outcome, including gestational age, Apgar scores, antenatal steroids, HMD, IVH, periventricular leukomalacia, PDA, BPD, and steroid use for BPD.

lactic indomethacin therapy on neurologic function in extremely preterm infants remain a concern owing to limited neurodevelopmental follow-up information.[7] Previous studies in animals and humans have demonstrated that prophylactic indomethacin, a cerebral vasoconstrictor, can diminish cerebral blood flow, dull adaptive vasodilatory responses, and may decrease cerebral oxygen delivery interfering with cerebral oxygen use.[8-10] Be-

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Table 1. Clinical Data of Study Patients*

Characteristic	Placebo (n = 37)	Indomethacin (n = 29)
Birth weight, g	846 ± 193	880 ± 196
Gestational age, wk	26.3 ± 1.8	26.2 ± 1.7
Males	54.1	58.7
Inborn	100.0	96.6
Antenatal steroids	59.5	62.1
Cesarean delivery	62.2	65.5
Maternal race, white	97.3	100.0
Apgar score, 1 min	5.8 ± 1.8	5.6 ± 1.9
Apgar score, 5 min	7.9 ± 1.4	7.9 ± 1.2
Chronological age, mo	37.4 ± 10.3	38.6 ± 7.3

*Values are given as percentages or mean ± SD.

Table 2. NICU Diagnosis of Patients Seen at 3 Years' CA*

Diagnosis	Placebo (n = 37)	Indomethacin (n = 29)	*P*
HMD	86.5	89.7	.70
Sepsis	18.9	13.8	.58
NEC	2.7	0	.32
PDA	48.6	27.6	.08
BPD	48.6	72.2	.05
BPD, postnatal steroids	46	69	.06
Days on ventilator	21.9	25.6	.44
IVH (grade 3 or 4) or PVL	21.6	17.2	.66

*NICU indicates newborn intensive care unit; CA, corrected age; HMD, hyaline membrane disease; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosis; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; and PVL, periventricular leukomalacia. Values are given as percentages.

cause other reports suggest that prophylactic indomethacin might increase the risk of neurodevelopmental handicaps in these susceptible infants, we now report the neurodevelopmental follow-up of all available survivors from our earlier study at approximately 3 years' corrected age (CA).

RESULTS

Forty-two (98%) of 43 infants who received prophylactic indomethacin survived compared with 46 (98%) of 47 who received placebo. Sixty-six (75%) of 88 surviving infants were seen for neurodevelopmental assessment at approximately 3 years' CA. Twenty-nine (69%) of 42 surviving infants who received prophylactic indomethacin and 37 (80%) of 46 placebo-treated infants comprised this group. Patient information regarding 66 subjects seen for neurodevelopmental assessment is given in **Table 1**. In addition, there were no differences in maternal education or chorioamnionitis between the 2 groups.

Of 66 subjects seen for neurodevelopmental assessment at approximately 3 years' CA, there were no significant differences in patient diagnosis (**Table 2**). In addition, there was no difference in the occurrence of intrauterine growth retardation between the 2 groups. Twenty-three (79%) of 29 infants in the prophylactic indomethacin group had normal neurodevelopmental assessments at approximately 3 years' CA compared with 26 (70%) of 37 placebo-treated infants. Four (14%) of 29 infants in the prophylactic indomethacin group were severely impaired, each with 1 of the following: spastic diplegia, spastic quadriplegia, cognitive delay, and considerable motor delay. Eight (22%) of 36 placebo-treated infants were found to be severely impaired, including 7 with spastic diplegia and 1 with microcephaly. Of the 40 available subjects at 36 months' CA who never experienced a PDA in the NICU, 17 (81%) of 21 infants who received prophylactic indomethacin had normal neurodevelopmental assessments compared with 12 (63%) of 19 placebo-treated infants ($P>.05$). Analysis based on ordered logistic regression (controlling for gestational age, Apgar scores, antenatal steroids, occurrence of HMD, IVH, periventricular leukomalacia, PDA, BPD, and BPD with steroid treatment) also indicated a higher risk of adverse neurodevelopmental outcome for placebo-treated infants than for those given prophylactic indomethacin, with an odds ratio of 1.64 (95% confidence interval, 0.53-5.26) ($P>.05$). The overall neurodevelopmental outcome is given in **Table 3**.

COMMENT

Prophylactic indomethacin is a synthetic indoleacetic acid derivative with pharmacologic activity similar to other nonsteroidal anti-inflammatory agents. Based on studies involving experimental animals, proposed mechanisms of action include scavenging of prostaglandin-mediated free radicals and/or hindering of active calcium transport in vascular smooth muscle.[9,15] These activities have been shown to result in the inhibition of the cyclooxygenase arm of prostaglandin synthesis and the reduction of both cerebral blood flow and reactive postasphyxial cerebral hyperemia.[16] Prophylactic indomethacin has been shown to be effective in closing established PDA in preterm infants.[17] In addition, when used within the first 24 hours of life as a prophylactic agent, indomethacin prevents PDA by promoting closure of the PDA[4,5] and decreases the incidence of severe (grade 3 and grade 4) IVH.[6] Despite several studies that demonstrate the immediate beneficial effects of prophylactic indomethacin toward prevention of PDA and severe IVH, its routine use has not been universally recommended because of limited long-term neurodevelopmental outcome data. Specific concerns have emerged from many animal and human studies that demonstrate prophylactic indomethacin decreases cerebral blood flow and may play a role in the development of ischemic brain injury and developmental handicaps.[10,18,19]

In assessing whether other effects of prophylactic indomethacin may be beneficial, Ment et al[20] demonstrated that prophylactic indomethacin decreased the incidence of IVH in response to a hemorrhagic hypotension-volume reexpansion insult in newborn beagle pups and promoted germinal matrix microvascular maturation.[21] Subsequently, in the largest prospective, randomized, placebo-controlled, multicenter trial involving 431 very low-birth-weight infants, Ment et al[6] reported that prophylactic low-dose indomethacin (a dose of 0.1 mg/kg

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Table 3. Neurodevelopmental Assessment of Available Subjects at Approximately 3 Years' Corrected Age*

Variable	All Subjects		Subjects Without PDA in NICU	
	Placebo	Indomethacin	Placebo	Indomethacin
No.	37	29	19	21
Corrected age, mo	33.8 ± 10.2	35.1 ± 7.2	36.6 ± 8.3	36.3 ± 4.8
Head circumference, cm	49.3 ± 2.1	49.6 ± 2.1	49.2 ± 1.9	49.3 ± 2.3
Neurodevelopmental assessment, %				
Normal	70.3	79.3	63.1	81.0
Mild to moderately abnormal	8.1	6.9	5.3	4.8
Severely impaired	21.6	13.8	31.6	14.2

*PDA indicates patent ductus arteriosus; NICU, newborn intensive care unit. Values are given as mean ± SD except where indicated. All P values were not significant.

administered intravenously at 6 to 12 postnatal hours and every 24 hours for 2 more doses) significantly decreased the incidence and severity of severe IVH and PDA.[6]

Ment et al[22] later reported the neurodevelopmental outcome at 36 months' CA of 343 surviving infants (86%) of 431 enrolled in the original IVH prevention trial. The overall survival rate was 92% (384/431); 8% of both groups developed cerebral palsy, and there were no significant differences in the occurrence of deafness, blindness, and Stanford-Binet Scale IQ scores. The authors concluded that prophylactic low-dose indomethacin, administered intravenously at an initial dose of 0.1 mg/kg at 6 to 12 hours of age and every 24 hours for 2 more doses to prevent IVH does not result in adverse cognitive or motor outcomes at 36 months' CA.

Earlier, we reported that a course of prophylactic low-dose indomethacin therapy, when initiated within 24 hours of birth, decreased ductal shunting in a randomized, prospective, controlled trial involving 90 infants with birth weights between 600 to 1250 g who received prophylactic surfactant in the delivery room.[4] Previous clinical trials involving prophylactic low-dose indomethacin for the prevention of PDA differed from our study in that all the infants in our study received prophylactic surfactant in the delivery room, had birth weights and gestational ages slightly less than those reported in previous studies, and received more prophylactic total-dose indomethacin (a dose of 0.1 mg/kg administered every 24 hours for 6 doses vs a dose of 0.1 mg/kg administered every 24 hours for 3 doses).[5,6] Our homogeneous population of low-birth-weight infants would be considered at highest risk for developing a hemodynamically significant PDA. Because they received more prophylactic total-dose indomethacin, the risk for adverse effects of prophylactic indomethacin on cerebral blood flow and the development of ischemic brain injury may have been increased.

When the 2 treatment groups were assessed based on the initial treatment randomization, overall neurodevelopmental outcome at approximately 3 years' CA in all available subjects was not adversely affected by prophylactic indomethacin administered at a dose of 0.1 mg/kg every 24 hours for 6 doses. In all available subjects, the prophylactic indomethacin group had identical head growth as measured by head circumference compared with placebo-treated infants. In all available subjects, 23 (79%) of 29 subjects in the prophylactic indomethacin group had a normal outcome compared with 26 (70%) of 37 infants receiving placebo ($P = .68$). Some of the infants randomized to either of the initial treatment strategies developed PDA and required therapeutic prophylactic indomethacin and/or surgical ligation resulting in several treatment subgroups. However, prophylactic indomethacin did not adversely affect the neurodevelopmental outcome of 40 infants who failed to develop PDA in the NICU and whose therapy differed only by blinded randomization to either prophylactic indomethacin or placebo treatment. Head growth for infants without PDA was the same for those who received prophylactic indomethacin compared with those who received placebo. Furthermore, 17 (81%) of 21 infants without PDA treated with prophylactic indomethacin had normal neurodevelopmental assessments at 36 months' CA compared with 12 (63%) of 19 placebo-treated infants. Fewer prophylactic indomethacin–treated infants were considered severely impaired, but this was not statistically significant. Compared with the placebo group, the prophylactic indomethacin group in our study had an increased occurrence of BPD. Although BPD is associated with poorer neurodevelopmental outcome, this finding did not adversely affect neurodevelopmental outcome in the prophylactic indomethacin group analyzed by ordered logistic regression, controlling for BPD.

Although prophylactic low-dose indomethacin initiated within the first 24 hours of life promotes closure of the PDA in extremely preterm infants, this treatment has not been shown to decrease other clinical outcome variables such as chronic lung disease, survival, total duration of hospital stay, or time to regain birth weight.[4] However, as recently recommended by Clyman[23] in an analysis of 4 different treatment strategies for PDA, prophylactic indomethacin treatment may be the most appropriate strategy to follow when the incidence of either grade 3 or grade 4 IVH or pulmonary hemorrhage is greater than 10% or when indomethacin failure and the need for surgical ligation exceeds 30%. If neonatologists determine that the use of early prophylactic low-dose indomethacin for the prevention of PDA and severe intracranial hemorrhage is a worthwhile strategy in their patient population, these data suggest that its use is not associated with adverse neurodevelopmental outcome.

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REFERENCES

1. Krovetz LJ, Rowe RD. Patent ductus, prematurity and pulmonary disease. *N Engl J Med*. 1972;287:513-514.
2. Thibeault DW, Emmanouilides GC, Nelson RJ, Lachman RS, Rosengart RM, Oh W. Patent ductus arteriosus complicating the respiratory distress syndrome in preterm infants. *J Pediatr*. 1975;86:120-126.
3. Alpan G, Clyman RI. Cardiovascular effects of surfactant replacement with special reference to the patent ductus arteriosus. In: Robertson B, Taeusch HW, eds. *Surfactant Therapy for Lung Disease: Lung Biology in Health and Disease*. Vol 84. New York, NY: Marcel/Dekker; 1995:531-545.
4. Couser RJ, Ferrara TB, Wright GB, et al. Prophylactic indomethacin therapy in the first twenty-four hours of life for the prevention of patent ductus arteriosus in preterm infants treated prophylactically with surfactant in the delivery room. *J Pediatr*. 1996;128:631-637.
5. Domanico RS, Waldman JD, Lester LA, McPhillips HA, Catrambone JE, Covert RF. Prophylactic indomethacin reduces the incidence of pulmonary hemorrhage and patent ductus arteriosus in surfactant-treated infants <1250 grams [abstract]. *Pediatr Res*. 1994;35:331A.
6. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics*. 1994; 93:543-550.
7. Fowlie PW. Prophylactic indomethacin: systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 1996;74:F81-F87.
8. Van Bel F, Van de Bor M, Stijnen T, Baan J, Ruys JH. Cerebral blood flow velocity changes in preterm infants after a single dose of indomethacin: duration of its effect. *Pediatrics*. 1989;84:802-807.
9. Leffler CW, Busija DW, Fletcher AM, Beasley DG, Hessler JR, Green RS. Effects of indomethacin upon cerebral hemodynamics of newborn pigs. *Pediatr Res*. 1985; 19:1160-1164.
10. McCormick DC, Edwards AD, Brown GC, et al. Effect of indomethacin on cerebral oxidized cytochrome oxidase in preterm infants. *Pediatr Res*. 1993;33:603-608.
11. Avery GB, Fletcher AB, Kaplan, Brudno DS. Controlled trial of dexamethasone in respirator-dependent infants with bronchopulmonary dysplasia. *Pediatrics*. 1985; 75:106-111.
12. Yaffe SJ, Friedmann WF, Rogers D, et al. The disposition of indomethacin in premature babies. *J Pediatr*. 1980;97:1001-1006.
13. Papile LS, Burstein J, Burstein R, et al. Incidence and evolution of the subependymal intraventricular hemorrhage: a study of infants with weights less than 1500 grams. *J Pediatr*. 1978;92:529-534.
14. Allan WC, Philip AGS. Neonatal cerebral pathology diagnosed by ultrasound. *Clin Perinatol*. 1985;12:195-216.
15. Northover BJ. Indomethacin: a calcium antagonist. *Gen Pharmacol*. 1983;8:293-296.
16. Dahlgren N, Nilsson B, Sakabe T, et al. The effect of indomethacin on cerebral blood flow and oxygen consumption in the rat at normal and increased carbon dioxide tensions. *Acta Physiol Scand*. 1982;III:475-485.
17. Heymann MA, Rudolph AM, Silverman NH. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. *N Engl J Med*. 1976; 295:530-535.
18. Mardourn R, Bejar R, Merritt TA, Berry C. Controlled study of the effects of indomethacin on cerebral blood flow velocities in newborn infants. *J Pediatr*. 1991; 118:112-115.
19. Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. *Lancet*. 1990;335:1491-1495.
20. Ment LR, Stewart WB, Scott DT, Duncan CC. Beagle puppy model of intraventricular hemorrhage: randomized indomethacin prevention trial. *Neurology*. 1983; 33:179-184.
21. Ment LR, Stewart WB, Ardito TA, Huang E, Madri JA. Indomethacin promotes germinal matrix microvessel maturation in the newborn beagle pup. *Stroke*. 1992; 23:1132-1137.
22. 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.
23. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. *J Pediatr*. 1996;128:631-637.

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