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Elective Procedures and Anesthesia in Children: Pediatric Surgeons Enter the Dialogue on Neurotoxicity Questions, Surgical Options, and Parental Concerns

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Abstract

The Pediatric Anesthesia NeuroDevelopment Assessment research group at Columbia University Medical Center Department of Anesthesiology has conducted biannual national Symposia since 2008 to evaluate study data and invigorate continued thinking about unresolved issues of pediatric anesthesia neurotoxicities. The third Symposium extended the dialogue between pediatric anesthesiologists and surgeons in panel presentations and discussions by four surgical specialists. This paper reports the prevailing opinions expressed by a pediatric general surgeon, urologist, plastic surgeon and ophthalmologist and explores factors related to delayed operative intervention, need for multiple procedures, and parental concerns.

Keywords

elective procedures; pediatric surgeons; anesthesia; children; neurotoxicity

Concerns for the possible neurotoxic and long-term neurodevelopmental effects of drugs commonly used for sedation and anesthesia in children prompted the Food and Drug Administration (FDA) in 2007 to challenge the anesthesiology community to provide input into their assessment of safety risks for these drugs.¹ Pre-clinical data accumulating since 2000 had demonstrated central nervous system changes in juvenile animal models after exposure to drugs commonly used in anesthesia and/or sedation for pediatric procedures.^{2–4}

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Applicability of laboratory data to human effects was hampered in the absence of clinical studies. Debate ensued about whether neuroapoptosis was the critical pathologic mechanism. There was limited information on specific agent and dose effects, as well as uncertainty about how to translate the window of vulnerability from animal to human development. In response to the FDA challenge, in the past 5 years, additional laboratory as well as retrospective and prospective clinical studies have been initiated and reported in the anesthesiology literature.

The Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) study group has conducted biannual Symposia to synthesize and evaluate study data and invigorate continued thinking about unresolved issues of pediatric anesthesia neurotoxicities. In the third Symposium, pediatric surgeons from 4 subspecialties were invited for the first time to consider the question of neurotoxicity and to contribute to the dialogue through a panel presentation and open discussion on the topic of elective procedures and anesthesia in children. This paper reports the prevailing opinions of surgeons within these surgical specialties and explores factors related to delayed operative intervention, need for multiple procedures, and parental concerns.

The panel comprised surgeons representing pediatric general surgery (R.A.C.), urology (P.C.), plastic surgery (J.A.A.), and ophthalmology (P.F.G.). The 4 panelists are board certified in their specialties and all hold academic appointments at their medical center–affiliated universities. They represent combined clinical practice experience of 71 years beyond residency, extensive involvement in their respective professional associations, and a cumulative total of over 120 journal articles and other peer-reviewed publications contributed to the literature. Panel was moderated by a physician board-certified in anesthesiology and pediatrics and with more than 30 years experience including expertise in neonatal anesthesia, fetal diagnosis and treatment, and pain management. Symposium attendees' questions to panelists, and their additional comments and discussions were synthesized by a core member of the PANDA team, who holds joint appointments and an endowed professorship in her University's Faculties of Nursing and Medicine (Department of Anesthesiology) (M.W.B.).

PANEL PRESENTATIONS

Inguinal Hernia

Inguinal hernia is one of the most common procedures performed by pediatric surgeons, with an estimated incidence rate of 0.8% to 4% of live births. With premature birth, the incidence rate of inguinal hernia can increase to 30%.⁵ When the processus vaginalis, an embryonic developmental outpouching of the peritoneum, remains patent, an inguinal hernia will likely develop. Tissue that normally resides within the peritoneal cavity, such as the intestine, can protrude through the inguinal hernia defect and become incarcerated, strangulated and progress to gangrene if the constriction is tight enough to compromise blood supply. The overall rate of 10% to 12% for incarceration of an existing hernia is increased to up to 31% in premature infants related to their developmental immaturity.³ Inguinal hernia carries risks of testicular (or ovarian) loss, intestinal ischemia and gangrene, recurrence, and complicated subsequent repairs.

Timing for surgical repair of inguinal hernia has been debated and has varied over time. Concern has been raised to balance the risks of anesthesia and surgery against the risk for incarceration and surgical complications. Delay in repair can result in edema and subsequent thickening of tissue around the hernia creating future technical surgical difficulties as well as chronic stretching of the hernia orifice with enlargement of the defect. In contrast, delay may allow the infant to become a better anesthetic candidate and to receive outpatient care. Suggested guidelines for the timing of surgery ranged from 44-week postconceptual age for infants born at term (> 37-wk gestation) to 60-week postconceptual age, with a weight >3.5 kg, for infants born before 37 weeks of gestation. For prematures, weight and age parameters have more recently given way to a trend to repair just before NICU discharge.⁵ This strategy allows for some resolution of comorbidities associated with prematurity, minimizes the risk of incarceration occurring after discharge to home, and allows for postanesthetic recovery within the NICU by a staff that knows the infant well. One surgeon compared inguinal hernia treatment and outcome data from 1 Canadian and 1 US tertiary care pediatric surgical center. Study results included a significantly increased rate of incarceration and number of emergency department visits for Canadian infants who waited for an average of 99 days after consultation and diagnosis when compared with US infants who underwent repair at an average of 21 days after diagnosis.⁶ This study highlights the risks of prolonged delay in inguinal hernia repair.

In this panelist's (R.A.C.) practice, parental questions about anesthesia and surgery have been around the baby's young age, as well as type of anesthesia and training of the anesthesiologist. Parents have not yet raised the question of potential for neurocognitive deficits. In response to questions initiated by parents, this surgeon provides reassurance that "specially trained anesthesiologists anesthetize small babies every day," that general anesthesia is often used but spinal anesthesia could be an option, and that the anesthesiologist will meet with the parent before surgery to discuss the risks of anesthesia and options for minimizing that risk.

Hypospadias and Undescended Testis

An experienced pediatric urologist (P.C.) reviewed 2 typical surgeries for which infant boys showed repair of hypospadias and of undescended testis (UDT). In both cases, timing of intervention remains a clinical question under consideration.

Hypospadias occurs in 1 in 250 male live births in the United States and is noted to be increasing in incidence and severity both in the United States and globally. Of infants born with the condition 8% have fathers and 14% have siblings suffering from the same condition. Phytoestrogens, vegan diets, and environmental pollutants have been etiologically implicated. Surgeons have been opting to perform the surgery at 6 months of age but there is a recent trend to perform initial surgery as early as 2 months. There are several reasons driving this change. Up to one quarter of surgeries reveal complications that require follow-up at a 6-month interval. It is best for all surgeries to be complete by the age of 2, when penile awareness and potty training begin. Healing is improved in the earliest months of infancy and in any case all surgeries should be well completed by the testosterone surge at the age of 3.

UDT or cryptorchidism is the most common genital abnormality occurring in 3% of full-term male infants and bilaterally for 15% of these cases. It differs from hypospadias in that it is not cosmetically obvious and spontaneous descent occurs for most in the first 6 months of life with the postnatal peak in androgens. Yet persistent UDT has serious clinical implications requiring treatment. By 6 months of age irreversible testicular changes may occur which suggests early surgical correction will improve fertility. Compared with testes in the unaffected male population, boys with UDT will have fewer germ cells at 6 months of age and delayed and defective germ cell maturation; its descended mate will have decreased fertility as well. With early surgical correction, associated hernias can be corrected, testicular torsion prevented, and examination for testis mass expedited, as well as the psychological effects of an empty scrotum eliminated. Histologic data for UDT, including decreased volume, decreased spermatogonia, and small seminiferous tubules, also support early treatment. Importantly, the lifetime risk of testis cancer with UDT is increased 4- to 7-fold over the annual rate for the general population,⁷ 10% of all testis tumors originate in UDT^{8,9} and UDT is 22 times more likely to become cancerous compared with testes in the general population. Although bringing down UDT does not mitigate an established cancer, it makes it possible to examine the testes. All these reasons have prompted the timing of treatment by 6 to 12 months with preference for 6 months relevant to the fertility issues.

Parental questions in this surgeon's (P.C.) practice have included concerns about neurocognitive delay related to the timing of surgery. Some parents have been bringing in published papers to discuss with the surgeon. Parental concerns vary by procedures with little concern around circumcision but questions were raised about delay for corrections of both hypospadias and UDT. This surgeon has been responding to parents' questions concerning neurocognitive effects of surgeries at an earlier age by explaining all answers are not yet known, but that the relative risk is probably quite small; "It is probably more dangerous driving to see (the surgeon) than to have anesthesia."

Cleft Lip and Craniosynostosis

The pediatric plastic surgeon (J.A.A.) panelist provided background on cleft lip and craniosynostosis, 2 common conditions for which procedures are performed during infancy.

Both conditions present with variations that may require multiple surgeries.

To improve the child's aesthetic appearance, especially from the parent perspective, repair of cleft lip is typically performed within the first 3 months of life. Delay beyond 3 months is associated with risks beyond aesthetics. Repair of the lip paves the way for subsequent cleft palate repair, which is important for development of speech, improved feeding, and hearing.

Craniosynostosis is the premature and abnormal fusion of 1 or more of the suture lines forming the human skull. As a result, head shape is distorted by aberrant bone growth patterns. Without correction this can lead to increased intracranial pressure and an abnormally shaped and asymmetrical craniofacial skeleton. Treatment is usually through frontocranial or vault reconstruction to restore the normal anatomy of the forehead and cranial vault, as applicable. The brain is thus allowed to expand and this force operates within functional matrix theory such that form follows function as bone is grown.¹⁰

Intracranial pressure values are elevated to higher levels in children who have several compared with one fused suture.¹¹

Frontocranial reconstructions are normally performed within the first 6 months of life to allow the brain to have adequate growth space and to utilize the force of brain push to grow bone. In a study of 123 children it was demonstrated that intracranial volume doubles by 9 months and triples by 6 years.¹² Early suture release also benefits adjacent structures as bone is more malleable earlier in life and reossification capacity is excellent for up to 1 to 2 years of age. At this age the child is probably unaware of any malformation. When repair is delayed there are serious consequences including increased risks of intracranial hypertension, the inability to take advantage of brain push, decreased reossification capabilities, and psychological effects on the child's self-image. The growing brain pushing on bones of the skull would usually foster bone growth, especially in suture areas, but this cannot occur where sutures are fused and the inability of bones to grow in one area may also lead to overgrowth in another area resulting in an abnormally shaped skull.

Parental concerns in this practice have focused on safety of anesthesia in general but specific concerns about neurocognitive effects have not been raised. Moreover, it is the surgical procedure rather than anesthesia that prompts questions asked.

Cataract Extraction and Strabismus

A senior surgeon in pediatric ophthalmology (P.F.G.) reviewed surgical interventions for cataract extraction, an emergency procedure for children, and for strabismus. Reminding listeners that the "...eye doesn't see; the brain sees...", this surgeon emphasized that the neurological connections implicit in the procedures including the very early critical period for development of vision as established by 1981 Nobel Prize winners David Hubel and Torsten Wiesel.

With a surgically eligible pediatric cataract no image can be formed on the macula and connections to the occipital cortex fail to develop. This makes cataracts in children a surgical emergency. Children with corneal transplant and glaucoma, furthermore, will have to undergo multiple surgeries and anesthesia exposures for suture removals and intraocular pressure measurements. Surgeries are usually limited to an hour they can only be done with anesthesia to keep the child immobile.

vision is a result of visual input. With esotropia one eye is seeing at a time; otherwise, overlapping images would occur. Amblyopia occurs with decreased cortical vision corresponding to the most frequently crossed eye. This is the indication for surgery and a more significant indicator than just the appearance of crossed eyes. Corrective surgery takes about 1 hour. Delay is not a viable option for esotropes. Vision in their occipital cortex and the use of binocularity, alignment, and development of stereopsis are the goals. There is consensus that delaying surgery brings consequences of a more unstable alignment, the stereopsis and binocularity becoming less achievable, and the amblyopia more entrenched.

Parent concerns, as expressed in this practice, focus on the immediate psychological impact of the surgery and whether the child will remember it. This surgeon (P.F.G.) reinforces that

the surgery is necessary, encourages parents to go forward, and shares that her own children have experienced anesthesia without obvious negative consequences. Potential for cognitive deficits have never been raised by these parents. Nevertheless, pediatric ophthalmology seems to be the first pediatric surgical specialty that has attempted to address this issue in its literature through report of a pilot study of 21 children undergoing strabismus surgery in South Korea.¹³ However, the authors' use of neurocognitive testing preoperatively and 4 weeks postoperatively in a sample of children aged 5 to 10 years does not address the concerns raised by animal and human epidemiological studies that suggested that vulnerability to anesthetic exposure is primarily in the developing brain and leads to long-term deficits at later stages of development.

SUMMARY OF PRESENTATIONS

This experienced group of surgeons in 4 pediatric surgical specialties reported on selected surgeries typically performed on young children. Across the presentations it was clear that delaying surgery is not a clinical option for some procedures and that for others delay is not a clear cut decision but a question of balancing risks. By agreeing to be panelists, all participants demonstrated their willingness to open the dialogue between the surgical and anesthesia communities on the unresolved question of potential for neurocognitive deficits related to anesthetic agent exposure for surgical procedures during a critical period of early brain development. Some expressed that the opportunity to discuss this content does not exist within their individual specialty conferences. Yet there was also an expressed frustration with the unknown components of this question. Surgeons were reluctant to raise this issue with parents beyond answering the questions posed by parents to the extent that answers are available. They hesitated to introduce fears to already concerned parents. In the absence of clear evidence, surgeons tended to refer the question back to anesthesiologists and to rely on them for discovering the answers. There was much sensitivity about transferring partial and inconclusive information to parents and to disturbing the parent/surgeon communication process. Both uncertainty and discomfort with the uncertainty were prevalent concerns. Surgeons also underscored the differences between surgical goals and anesthesia goals. While the latter are responsible for having the patient "wake up safe," the surgeons are aiming for both safe and optimum results for the surgical procedure. This can extend to the choice of anesthesia that assures no patient motion or interference with the surgical field and no delayed scheduling that reduces the likelihood of the procedure's success.

DISCUSSION: SYMPOSIUM AUDIENCE DIALOGUE WITH PANELISTS

Questions raised after the panel presentations concerned the need for more data, the meaning of delay, the role of individual or multiple anesthetic exposures, and the reality of increasing survival of early prematurity as a risk factor for neurodevelopmental abnormalities. Surgeons and anesthesiologists agreed that more data are needed on duration, dose and repetition of anesthetic events, and their effects on neurological outcomes. The question was raised concerning what comprises a short anesthesia and how multiple short anesthesia exposures compare to a single prolonged exposure. Answers to these critical questions remain to be elucidated. Although it was agreed that improved coordination of care could

allow for fewer exposures to anesthetic agents, it is not yet known whether one longer exposure carries less risk than several shorter ones nor what the maximum duration associated with minimum risk might be.

Several areas in which more evidence is needed mirrored the list of concerns aired at the first PANDA Symposium 4 years before as well as concurrent concerns in the literature. These included the need to hone in on elements of concern from animal models while also determining the critical time frame and conditions for humans and the unique human domains, such as expressive language, that need to be included as study endpoints. The need to translate age of vulnerability across species remains critical and there is continued suggestions that human prenatal period corresponds to the sensitive periods in animal models and has been understudied in humans. Incomplete understanding of the underlying mechanisms for neurotoxicity persists.

Anesthesia practices have advanced rapidly and may render many retrospective study findings obsolete with regard to the agents used.¹⁴ Symposium panelists and audience discussants pointed out that morbidity will continue to confound the anesthesia exposure question, especially for the increasing numbers of extremely premature infants. Likewise there are subsets of children with conditions necessitating multiple surgeries and with comorbidities that will make it difficult to separate the effects of anesthesia from the impacts of pathologic changes related to underlying disease processes over time. To overcome the many barriers to the meaningful study of neurocognitive effects of children undergoing anesthesia, it was recommended that concurrent bench and clinical studies be pursued. Animal studies can uncover underlying mechanisms for neurotoxicity and further determine the effects of various classes of drugs. Until more definitive conclusions can be drawn regarding the relative impact of various anesthetic and sedative drugs on neurodevelopment in young humans, total avoidance of any one class of drug cannot be recommended. The merits of using regional (spinal or caudal) anesthesia as much as possible were discussed. It was suggested that balanced anesthetic techniques be utilized and developed in which regional or nerve block techniques and both opioid and nonopioid supplemental analgesics be used to allow reduction of the amount of volatile agents and sedatives needed.

This innovative panel opened a discussion between anesthesiologists and selected surgical subspecialists on the thorny question of anesthetic agents' potential for lasting neurocognitive impairment in children who undergo surgery during their early development. There is a need to continue this dialogue as well as to expand it to the range of other providers who order procedures that require anesthesia or sedation.

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