Anestesia Segura en el Paciente Frágil: Neonato y Feto. Neurotoxicidad. Solo Cuestión de Fármacos?

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No tengo ninguna afiliación a casas comerciales, compañias farmacéuticas ni nada que pudiera afectar el contenido de esta presentación

U.S. Department of Health and Human Services

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- Drug Alerts and Statements
- Medication Guides
- Drug Safety Communications

FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women

Diciembre 2016

- **No esta claro que estos efectos negativos en el comportamiento o en los procesos de aprendizaje son debido a medicamentos o a la condición medica del paciente o a otras cosas…**

Young Brain and Anesthesia: Refusal of Anesthesia Is Not an Option!

Deborah J. Culley, M.D., Michael J. Avram, Ph.D.

TWENTY-FIVE years ago, surgery was commonly performed on awake or paralyzed infants and children without the benefit of analgesics, sedatives, or anesthetics. This practice was justified by a fear that these drugs would increase the risk of adverse surgical outcomes and the belief that infants did not experience pain.[1] Subsequent clinical studies have demonstrated that inadequate sedation, anesthesia, and analgesia may actually increase the risk of adverse postoperative outcomes in infants and children and have led to a paradigm shift such that the use of general anesthetics and analgesics is now routine in the humane practice of pediatric anesthesiology.[1–3] This does not mean that doing so is without risk or controversy. Seven years after this change, questions began to arise from the laboratory of John Olney, M.D., who was well known for his work on fetal alcohol syndrome, suggesting that exposure

"…[T]here may be risk associated with exposure to general anesthesia…[but] surgery without adequate anesthesia and analgesia is simply not an option."

with enhanced apoptosis (neurons and glia) and alterations in neurogenesis, gene expression, cytokine expression, synaptic transmission, and lipid metabolism that are, in turn, associated with cognitive and behavioral abnormalities in later life.[7] Perhaps the most interesting of these findings is that they appear to be dependent on developmental stage and duration of treatment. Administration of a single anesthetic to rodents or subhuman primates for long durations (6 h or more) or multiple shorter treatments during critical periods of development are crucial for the development of these changes. Studies in rodents that have looked at shorter exposures to general anesthetics during these same critical developmental periods have found acute but not long-lasting changes in synapse density or function, neurogenesis, and cell survival and differentiation, and no differences in cognitive perfor-

Anesthesiology : Abril 2018

Ya sabemos…

- Bouza H. The impact of pain in the immature brain. J Maternal-Fetal Neonat Med 2009
- Infantes y neonatos definitivamente experimentan dolor y estrés
- Retener analgesia y sedación puede causar hiperalgesia, alteraciones estructurales y comportamientos inapropiados en el desarrollo posterior

Data Pre-Clínica

- Animales
- Trasladar la evidencia en animales a humanos es una ciencia inherentemente imprecisa

Anesthesiology 2005; 102:866-8

Of Mice and Men: Should We Extrapolate Rodent Experimental Data to the Care of Human Neonates?

Sulpicio G. Soriano, M.D.,* Kanwaljeet J. S. Anand, M.B.B.S., D.Phil., Cynthia R. Rovnaghi, M.S., Paul R. Hickey, M.D.
* Children's Hospital Boston and Harvard Medical School, Boston,

Lin EP, et al
Neurotoxicology Teratology 2017

- Revisión de 440 estudios pre-clínicos
- Mayor proporción de estudios—anormalidades con exposiciones de duración más larga
- No se difinió una línea demarcadora en tiempo
- Tampoco se definió edad

Estudios Clínicos en Humanos

6 Estudios principales

- PANDA
- GAS
- T-Rex
- MASK
- UCSF
- CUMC

MASK

Mayo Safety in Kids

Neuropsychological and Behavioral Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia

The Mayo Anesthesia Safety in Kids (MASK) Study

David O. Warner, M.D., Michael J. Zaccariello, Ph.D., L.P., Slavica K. Katusic, M.D., Darrell R. Schroeder, M.S., Andrew C. Hanson, B.S., Phillip J. Schulte, Ph.D., Shonie L. Buenvenida, R.N., Stephen J. Gleich, M.D., Robert T. Wilder, M.D., Juraj Sprung, M.D., Danqing Hu, M.D., Robert G. Voigt, M.D., Merle G. Paule, Ph.D., John J. Chelonis, Ph.D., Randall P. Flick, M.D., M.P.H.

Anesthesiology Julio 2018

MASK

- Estudio observacional
- Retrospectivo y Prospectivo
- Niños de Minnesota
- Una anestesia, múltiples anestesias, o no anestesia antes de los 3 años
- Estudios neurocognitivos en grupo prospectivo

Estudio Retrospectivo

- Anestésicos multiples pueden aumentar la frecuencia de problemas de aprendizaje y de TADH (déficit de atención)

Estudio Prospectivo Anesthesiology Julio 2018

- Anestesia antes de los 3 años no fue asociada a deficits en inteligencia general que era el resultado primario
- Una única exposición no llevó a ningún deficit neuropsicológico
- Múltiples exposiciones se asoció a disminuciones en el procesamiento de la coordinación motora y de velocidad

Confounding Factors (factores que confunden)

Cuando otro factor influye directamente tanto en la necesidad de anestesia como en el resultado de neurodesarrollo

Raikkonen K et al
Am J of Epidemiology 2017

- Consumo materno de regaliz durante el embarazo
- Consecuencia cognitiva y psiquiátrica en niños
- Disminución en la inteligencia
- Aumento en la frecuencia de ADHD (trastorno de atención e hiperactividad)

Peterson BS
JAMA Psychiatry 2015

- Relación contaminantes atmosféricos y el desarrollo de la materia blanca en el cerebro y el desarrollo cognitivo
- Exposición en útero
- Múltiples problemas en el desarrollo neurológico

- Procedimiento o cirugía
- Morbilidad que afecta directamente el desarrollo neurológico
    - Prematuridad
    - Síndromes
    - Anormalidades cromosómicas
    - Parálisis cerebral

- Niños con problemas en la audición
- Niños con bajo nivel socioeconómico- problemas dentales
- Niños con problemas de comportamiento
- Cirugía mayor- > respuesta inflamatoria afectando el cerebro

Otros Factores Perioperatorios

- Dolor
- Hipo-perfusión cerebral
- Hipoxia
- Disturbios electrolíticos
- Etc…

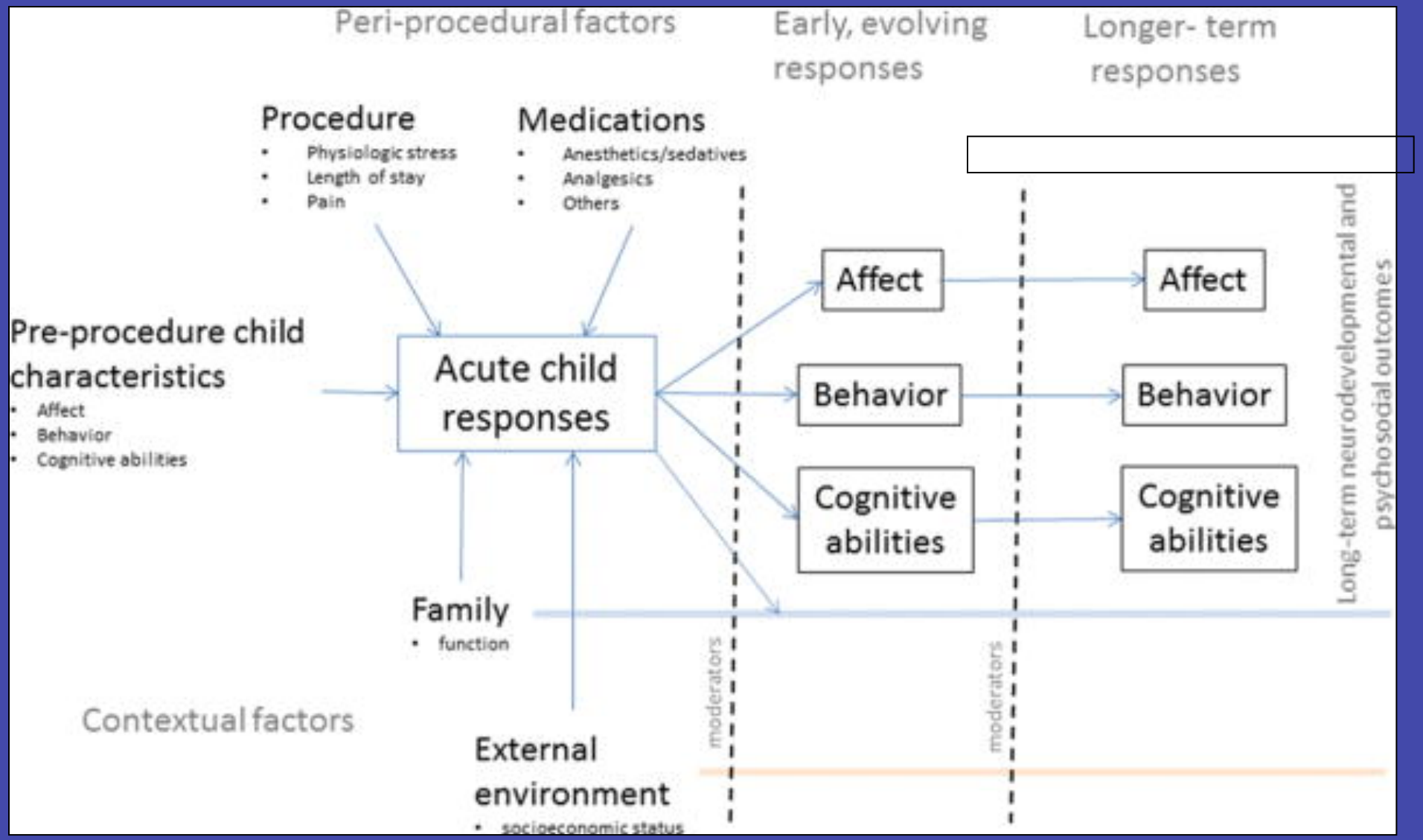


Fig. 1 . Example of a conceptual framework describing potential factors that affect outcomes after procedures requiring anesthesia. Periprocedural and contextual factors interact to determine acute child responses to the procedure; early and longer-term responses in affect, behavior, and cognitive abilities continue to be moderated by these contextual factors as they evolve.

Anesthesiology 2018

Estrategias Neuroprotectoras

Fármacos Neuroprotectores

- Eritropoyetina *
- Bumetanide
- L-carnitina- Toxicol Sci 2013 (luego de ketamina en ratas)
- Xenon*
- Dexmedetomidina*
- Melatonina
- Litio- BJA 2013 (luego de ketamine en ratas)

* Mejoras en los efectos cognitivos negativos de la anestesia neonatal en ratas

Neuroprotective effects of dexmedetomidine against glutamate agonist-induced neuronal cell death are related to increased astrocyte brain-derived neurotrophic factor expression.

Degos V1, Charpentier TL, Chhor V, Brissaud O, Lebon S, Schwendimann L, Bednareck N, Passemard S, Mantz J, Gressens P.

Anesthesiology May 2013

A Comparison of Caudal Epidural in Conjunction with Intravenous Dexmedetomidine Administration to Spinal Anesthesia in Preterm Infants Undergoing Awake Abdominal & Urologic Procedures

R Bryskin M.D., G Felema M.D., F Zayas-Bazan M.D.

Department of Anesthesiology-Nemours Children's Clinic/Wolfson Children's Hospital

Introduction: Anesthetic management of preterm neonates is often challenging secondary to co-morbidities associated with prematurity. The neonatal central and musculoskeletal respiratory systems are sensitive to the depressant effects of general anesthesia(GA) and result in prolonged need for assisted ventilation, and increased incidence of post-operative apnea/bradycardia(AB).(1,2) The use of spinal anesthesia(SA) in neonates has previously been demonstrated to be a safe and effective alternative to GA with reduced risk of postoperative respiratory complications. However, it has not gained wide acceptance due to its placement difficulty, high failure rate, and inability to accommodate surgical procedures >1hr.(3) Caudal anesthesia(CA) is a technically easier technique to perform and provides the ability (via threading of an angio-catheter or an epidural catheter) to extend both duration and dermatomal coverage to meet surgical demands. Regardless of the regional technique, supplemental intraoperative sedatives (Whiskey nipple, Ketamine, NO2, and Propofol) are frequently required to assist with block placement or to calm an agitated patient. Unfortunately, the use of these GABA and NMDA agents can lead to AB and has been suggested to cause neuronal apoptosis.(4,5) Dexmedetomidine(DEX) use in neonatal cardiac surgery population has been gaining popularity and is considered to provide a neuroprotective effect with a wide safety margin.

Hypothesis: The aim of this project was to determine if placement of a caudal epidural catheter and concomitant use of Precedex (CAD) had equivalent post surgical outcomes compared to SA performed on preterm infants undergoing abdominal and/or urologic procedures.

Retrospective Chart review
28 preterm infants

IHR, G-tube, Circ, Scrotal Surgeries
(Jan 2010-Sept 2014)

Comparable demographic variables and comorbidities
No statistical difference in birth weight, weight at the time of operation, mean gestational age, or post-conceptual age

SA group-16 pts	CAD group-12 pts
Whiskey Nipple(16/16 pts)	Dexmedetomidine
Ketamine IV (#/16 pts)	0.5 mcg/kg -> 0.5mcg/kg/hr
Spinal: 22G needle	Caudal: 22G Angiocath (10 pts)
Tetracaine 1% w/epi	18G w/Epidural Catheter (2 pts)
Dose of 0.6mg-0.8mg/kg	Ropiv/Bupiv 2.5-3mg/kg
	Caffeine IV 15mg/kg
	Tylenol PR 30 mg/kg

Placement Attempts

1st: 10/16 pts	1st: 11/12 pts
2nd: 1/16 pts	2nd: 1/12 pts
3rd: 3/16 pts	* includes 2 failed SA pts
4th: 2/16 pts	

Intra-Op Course

Surgical Duration: 42 min	Surgical Duration: 63 min
Apnea Episodes: 4	Apnea Episodes: 0
Bradycardia Episodes: 4	Bradycardia Episodes: 0

Post-Op Course-24 hrs

Apnea Episodes: 0	Apnea Episodes: 0
Bradycardia Episodes:5 pts	Bradycardia Episodes: 0
Supplemental Opioids: 0	Supplemental Opioids: 1 pt

Discussion: Although both awake SA and CA avoid the use of GA, supplementation with a potentially neurodegenerative sedative is not uncommon and may contribute to an increased incidence of post-operative AB. We found that the addition of DEX to CA provided for satisfactory surgical conditions in all patients without increasing the peri-operative risk of AB or contributing to hemodynamic instability. In comparison, 1/16 SA pts experienced intra-operative AB and 4/16 had bradycardia in the post-op period.

The choice of DEX as a sedative agent during CA carries the advantage of minimizing exposure to potentially neurotoxic sedatives plus the neuroprotective properties of DEX set it apart as an ideal agent for use in premature infants.(6,7) IV DEX has been previously noted in adult studies to provide a twofold effect in the setting of neuraxial blockade, both by prolonging the local anesthetic duration and providing intra-op sedation (ref).

One of the most significant advantages we observed in this study with the CAD approach is the prolongation of the surgical time that is allowed through local anesthetic re-dosing. The extension in surgical duration and possible dermatomal coverage have been welcomed by our surgical colleagues.

Conclusion: We report potential advantages to using CAD in preterm neonates. This approach provided for ease of placement, allowed extension of surgical duration, avoided potentially neurotoxic sedative agents, extended dermatomal coverage, and reduced incidence of AB in preterm neonates. For these reasons, we recommend CAD as a preferred awake regional technique for premature infants undergoing abdominal and urologic procedures.

References:

1- Cote CJ, et al. Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. Anesthesiology. 1995;82(4):809-22.
2- Krane EJ, et al. Postoperative apnea, bradycardia, and oxygen desaturation in formerly premature infants: prospective comparison of spinal and general anesthesia. Anesthesia and analgesia. 1995;80(1):7-13.
3- William JM,et al. Post-operative recovery after inguinal herniotomy in ex-premature infants: comparison between sevoflurane and spinal anaesthesia. British journal of anaesthesia. 2001;86(3):366-71.
4- Fredriksson A, at al. Neonatal exposure to a combination of N-methyl-D-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology. 2007;107(3):427-36.
5- Ibla JC, et al. Prolonged exposure to ketamine increases brain derived neurotrophic factor levels in developing rat brains. Current drug safety. 2009;4(1):11-6.
6- Duan X,et al. Dexmedetomidine provides neuroprotection: impact on ketamine-induced neuroapoptosis in the developing rat brain. Acta anaesthesiologica Scandinavica. 2014;58(9):1121-6.
7- Li Y, et al. Dexmedetomidine reduces isoflurane-induced neuroapoptosis partly by preserving PI3K/Akt pathway in the hippocampus of neonatal rats. PloS one. 2014;9(4):

Ventajas Técnica de Caudal con Dexdemetomidina

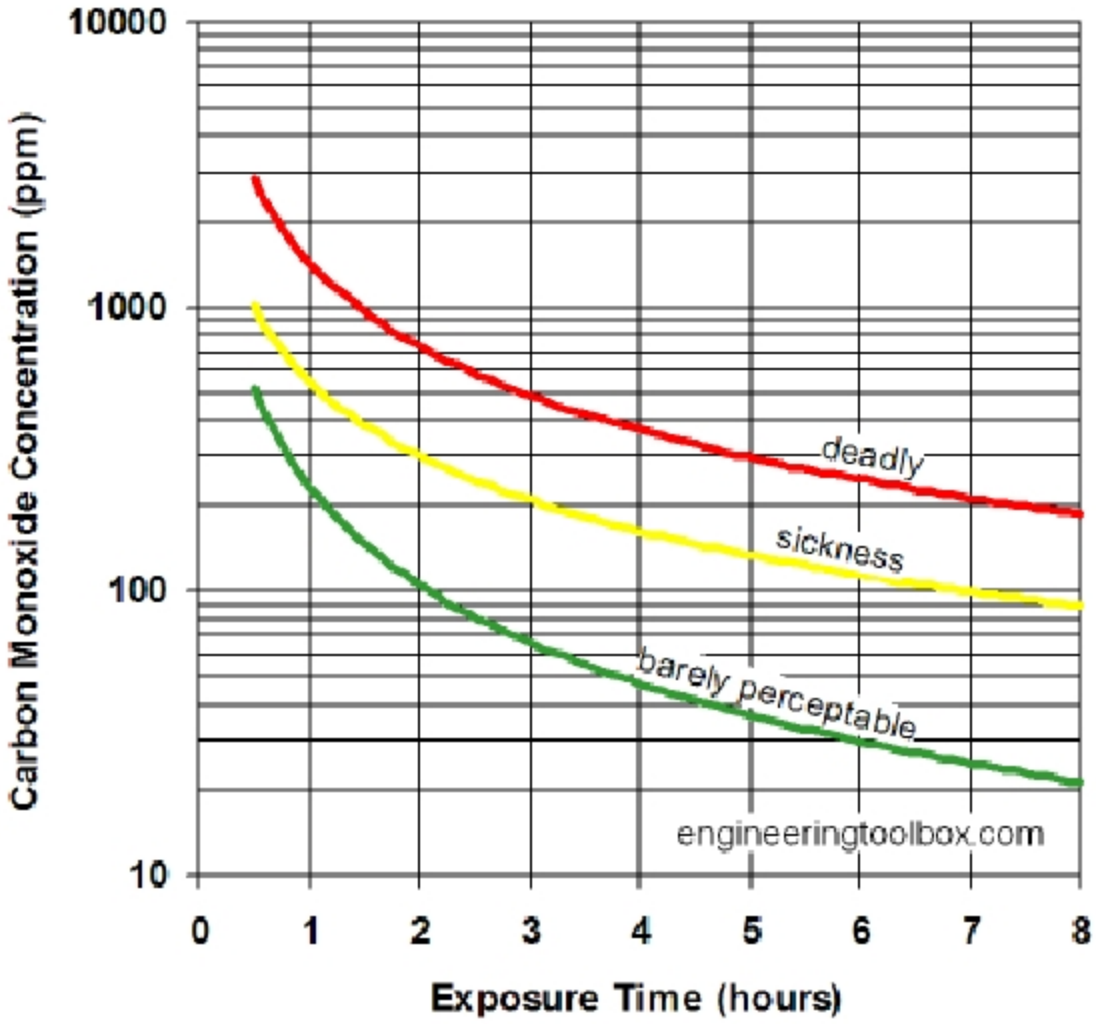
- Mayor duración de anestesia quirúrgica (con o sin catéter)
- Se evitan posibles agentes sedantes neurotóxicos
- Aumento de la cobertura en los dermatomas
- Reducción en la apnea/bradicardia en prematuros

Otros

- Yonamine et al, Anesthesiology 2013- añadiendo hidrógeno al anestésico inhalatorio puede disminuir la apoptosis por el sevo y los efectos de comportamiento (estudio en ratas)
- Zhao et al, Anesthesiology 2013– 1 hr pre-acondicionamiento con Isoflurano (puede disminuir el efecto neurotóxico de una exposicion posterior mas prolongada al isoflurano)

- Boscolo et al, BJA 2013– pramipexole (droga que restora la integridad mitocondrial)

Monóxido de Carbono
Toxicidad vs Agente Terapéutico



Coburn-Forster-Kane Model

$$\frac{d[COHb]_t}{dt} = \frac{\dot{V}_{CO}}{V_b} + \frac{1}{V_b\beta}\left(P_I CO - \frac{[COHb]_0 P_{\bar{c}} O_2}{[O_2Hb]M}\right)$$

La producción de CO
en los circuitos anestésicos de ventilación
fué reportado por primera vez en 1990

Moon RE, el al; *Anesthesiology*. 1990;73:A109.

Ventilación con CO

Puede prevenir la apoptosis neuronal inducida por la anestesia en el cerebro en desarrollo?

Cheng Y, Levy R
Anesthesia &Analgesia 2014

Subclinical Carbon Monoxide Limits Apoptosis in the Developing Brain After Isoflurane Exposure

Anesthetists rather than anesthetics are the threat to baby brains

Weiss M et al

Pediatric Anesthesia Oct 2013

Cerebro Inmaduro…

- Los infantes son vulnerables a daños neurotóxicos e isquémicos durante la anestesia y cirugía
- Es esencial que el anestesiólogo mantenga una perfusión cerebral óptima (a pesar de enfermedades co-existentes, efectos depresivos de los anestésicos, perturbaciones quirúrgicas, etc…)

Recordar…

Hipotensión- poco se sabe de la autoregulación cerebral en el neonato…qué presión arterial es adecuada para prevenir la isquemia cerebral en neonatos ?

Lo Nuevo en el 2018…

Ciencias Básicas

SCIENTIFIC REPORTS

OPEN

Caffeine Augments Anesthesia Neurotoxicity in the Fetal Macaque Brain

Received: 14 November 2017
Accepted: 14 March 2018
Published online: 28 March 2018

Kevin K. Noguchi[1], Stephen A. Johnson[2], Francesca M. Manzella[3], Kobe L. Masuoka[4], Sasha L. Williams[1], Lauren D. Martin[1], Gregory A. Dissen[5], Chrysanthy Ikonomidou[7], Katie J. Schenning[8], John W. Olney[1] & Ansgar M. Brambrink[9]

Caffeine is the most frequently used medication in premature infants. It is the respiratory stimulant of choice for apnea associated with prematurity and has been called the silver bullet in neonatology because of many proven benefits and few known risks. Research has revealed that sedative/anesthetic drugs trigger apoptotic death of neurons and oligodendrocytes in developing mammalian brains. Here we evaluated the influence of caffeine on the neurotoxicity of anesthesia in developing nonhuman primate brains. Fetal macaques (n = 7–8/group), at a neurodevelopmental age comparable to premature human infants, were exposed in utero for 5 hours to no drug (control), isoflurane, or isoflurane + caffeine and examined for evidence of apoptosis. Isoflurane exposure increased apoptosis 3.3 fold for neurons and 3.4 fold for oligodendrocytes compared to control brains. Isoflurane + caffeine caused neuronal apoptosis to increase 8.0 fold compared to control levels but did not augment oligoapoptosis. Neuronal death was particularly pronounced in the basal ganglia and cerebellum. Higher blood levels of caffeine within the range considered therapeutic and safe for human infants correlated with increased neuroapoptosis. Caffeine markedly augments neurotoxicity of isoflurane in the fetal macaque brain and challenges the assumption that caffeine is safe for premature infants.

Neurodevelopmental deficits are prominent among survivors of premature birth, particularly those born with a very low birth weight (<1500 grams; VLBW). Fifty percent of VLBW infants demonstrate impaired academic achievement and behavioral disorders[1] while brain imaging has revealed increased CSF volume (indicative of loss of brain mass) in addition to prominent reductions in cerebral cortical grey matter and deep nuclear grey matter[2]. Interestingly, birth prior to 32 weeks gestation is associated with a significant alteration in grey matter structure and adverse neurodevelopmental outcomes at 1 year of age. Pathophysiology of abnormal brain volumes and structure in VLBW infants is likely multifactorial and in most cases the etiologic factors remain unknown. Notably, new concerns have emerged that iatrogenic contributions may alter the normal developmental trajectory of the brain.

Sedative, anesthetic, and anti-epileptic[3–7] drugs (SADs) frequently used in neonatal medicine can trigger widespread apoptosis of neurons and oligodendrocytes in the developing brain of several animal species (including non-human primates) and produce long-term neurodevelopmental impairment[8–17]. Whether anesthetics produce similar toxicity in humans is still heavily debated and is supported by some clinical studies[1,3–7] but not others[18–21]. However, in December 2014 the Federal Drug Administration required eleven commonly used SADs to include labels warning drug exposure exceeding 3 hours may harm the developing brain. This change surprised many

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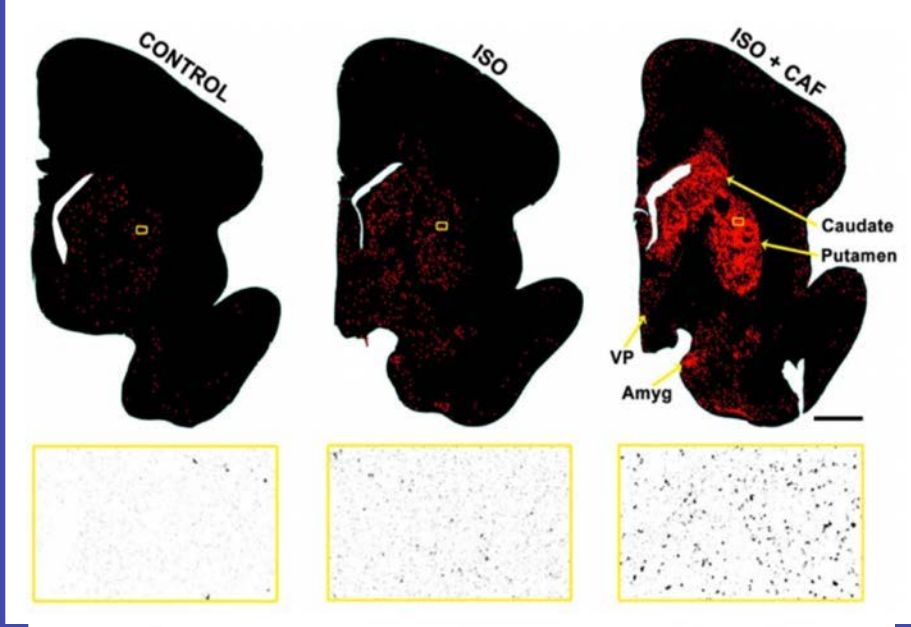
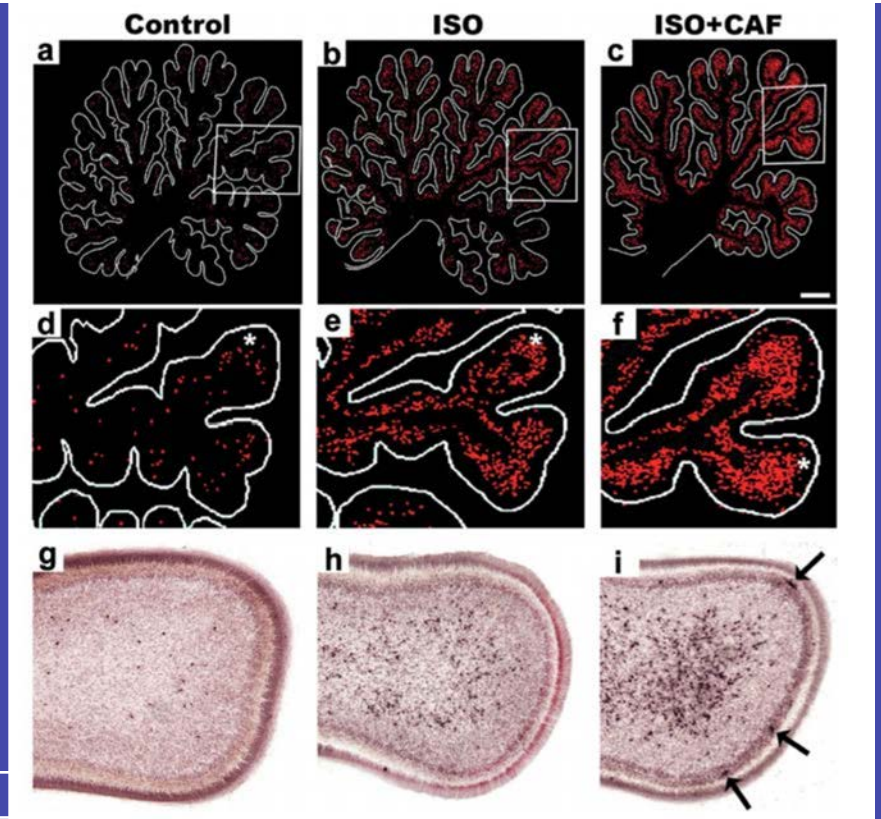
- Fetos Macacos, 5h expuestos a iso vs. iso + cafeina *en útero*
- Niveles en sangre considerados terapéuticos relacionados con apoptosis
- Aumento en la apoptosis:

	Iso	Iso + Caffeine
Neuronas	↑3.3-fold	**↑8-fold**
Oligodendrocitos	↑3.4-fold	No aumentaron

Noguchi KK et al. . Sci Rep. 2018 Mar 28;8(1):5302.





Noguchi KK et al. . Sci Rep. 2018 Mar 28;8(1):5302.

BJA

British Journal of Anaesthesia, 120 (3): 546–554 (2018)
doi: 10.1016/j.bja.2017.11.089
Advance Access Publication Date: 27 January 2018
Neuroscience and Neuroanaesthesia

Effects on adult cognitive function after neonatal exposure to clinically relevant doses of ionising radiation and ketamine in mice

S. Buratovic[1,*], B. Stenerlöw[2], S. Sundell-Bergman[3], A. Fredriksson[1], H. Viberg[1], T. Gordh[4] and P. Eriksson[1]

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Abstract

Background: Radiological methods for screening, diagnostics and therapy are frequently used in healthcare. In infants and children, anaesthesia/sedation is often used in these situations to relieve the patients' perception of stress or pain. Both ionising radiation (IR) and ketamine have been shown to induce developmental neurotoxic effects and this study aimed to identify the combined effects of these in a murine model.

Methods: Male mice were exposed to a single dose of ketamine (7.5 mg kg^{-1} body weight) s.c. on postnatal day 10. One hour after ketamine exposure, mice were whole body irradiated with 50–200 mGy gamma radiation (^{137}Cs). Behavioural observations were performed at 2, 4 and 5 months of age. At 6 months of age, cerebral cortex and hippocampus tissue were analysed for neuroprotein levels.

Results: Animals co-exposed to IR and ketamine displayed significant ($P<0.01$) lack of habituation in the spontaneous behaviour test, when compared with controls and single agent exposed mice. In the Morris Water Maze test, co-exposed animals showed significant ($P<0.05$) impaired learning and memory capacity in both the spatial acquisition task and the relearning test compared with controls and single agent exposed mice. Furthermore, in co-exposed mice a significantly ($P<0.05$) elevated level of tau protein in cerebral cortex was observed. Single agent exposure did not cause any significant effects on the investigated endpoints.

Conclusion: Co-exposure to IR and ketamine can aggravate developmental neurotoxic effects at doses where the single agent exposure does not impact on the measured variables. These findings show that estimation of risk after paediatric low-dose IR exposure, based upon radiation dose alone, may underestimate the consequences for this vulnerable population.

Keywords: cognition; gamma rays; ketamine; mice; tau proteins

Editorial decision: November 10, 2017. **Accepted:** November 30, 2017

- 10 ratas:
  - 7.5 mg/kg ketamine
  - Además de 50-200 mGy gamma radiación
- Morris laberinto de agua@ 2, 4, y 5 meses de edad
- 6meses de edad: análisis de hipocampo y corteza para análisis de proteina

Buratovic S. Br J Anaesth. 2018 Mar;120(3):546-554.

BJA

British Journal of Anaesthesia, 120 (3): 546–554 (2018)
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Advance Access Publication Date: 27 January 2018
Neuroscience and Neuroanaesthesia

Effects on adult cognitive function after neonatal exposure to clinically relevant doses of ionising radiation and ketamine in mice

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Keywords: cognition; gamma rays; ketamine; mice; tau proteins

Editorial decision: November 10, 2017. **Accepted:** November 30, 2017

- Animales co-expuestos:
  - Falta significativa de costumbre al medio ambiente
  - Fallos en la memoria y aprendizage
  - Elevada proteina tau en la corteza

Buratovic S. Br J Anaesth. 2018 Mar;120(3):546-554.

BJA

British Journal of Anaesthesia, 120 (4): 768–778 (2018)
doi: 10.1016/j.bja.2017.12.039
Advance Access Publication Date: 5 February 2018
Neuroscience and Neuroanaesthesia

A neurosteroid analogue with T-type calcium channel blocking properties is an effective hypnotic, but is not harmful to neonatal rat brain

N. Atluri[1,7], S. M. Joksimovic[1,7], A. Oklopcic[6], D. Milanovic[5], J. Klawitter[1], P. Eggan[1], K. Krishnan[3], D. F. Covey[3,4], S. M. Todorovic[1,2] and V. Jevtovic-Todorovic[1,*]

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[7] These authors made equal contributions.

This article is accompanied by an editorial. Quest for new drugs: a way to solve anaesthesia neurotoxicity? By Vutskits & Soeyd, Br J Anesth 2018;120:619–621, doi: 10.1016/j.bja.2018.01.004.

Abstract

Background: More than 4 million children are exposed annually to sedatives and general anaesthetics (GAs) in the USA alone. Recent data suggest that common GAs can be detrimental to brain development causing neurodegeneration and long-term cognitive impairments. Challenged by a recent US Food and Drug Administration (FDA) warning about potentially neurotoxic effects of GAs in children, there is an urgent need to develop safer GAs.

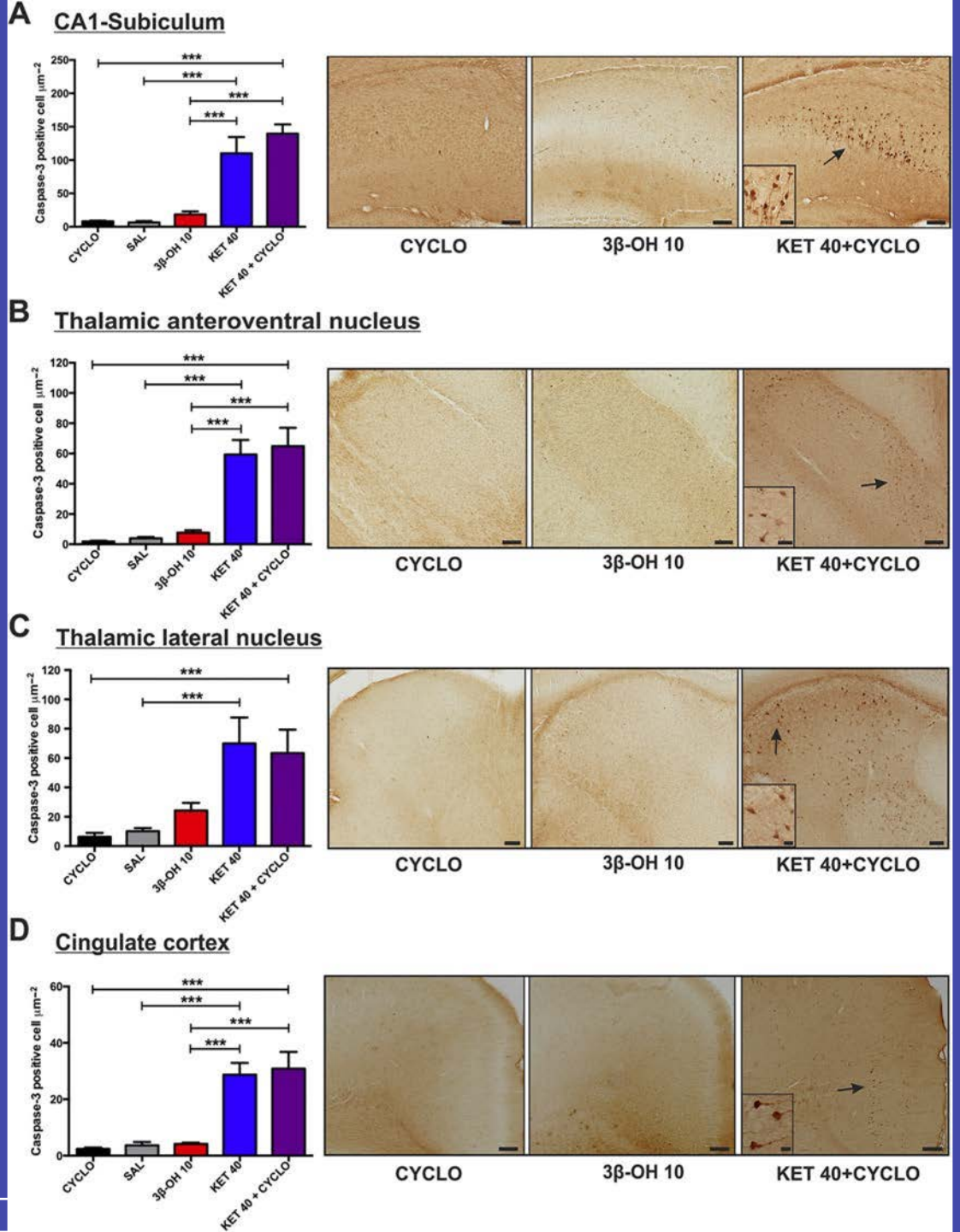
Methods: Postnatal Day 7 (P7) rat pups of both sexes were exposed to six (repeated every 2 h) injections of equipotent hypnotic doses of ketamine or the neuroactive steroid (3β,5β,17β)-3-hydroxyandrostane-17-carbonitrile (3β-OH) for 12 h. Loss of righting reflex was used to assess hypnotic properties and therapeutic index; quantitative caspase-3 immunohistochemistry was used to assess developmental neuroapoptosis; patch-clamp recordings in acute brain slices were used to assess the effects of 3β-OH on neuronal excitability and synaptic transmission. Cognitive abilities of rats exposed to ketamine, 3β-OH, or vehicle at P7 were assessed in young adulthood using the radial arm maze.

Results: The neuroactive steroid 3β-OH has a therapeutic index similar to ketamine, a commonly used clinical GA. We report that 3β-OH is safe and, unlike ketamine, does not cause neuroapoptosis or impair cognitive development when administered to P7 rat pups. Interestingly, 3β-OH blocks T-type calcium channels and presynaptically dampens synaptic transmission at hypnotically-relevant brain concentrations, but it lacks a direct effect on γ-aminobutyric acid A or glutamate-gated ion channels.

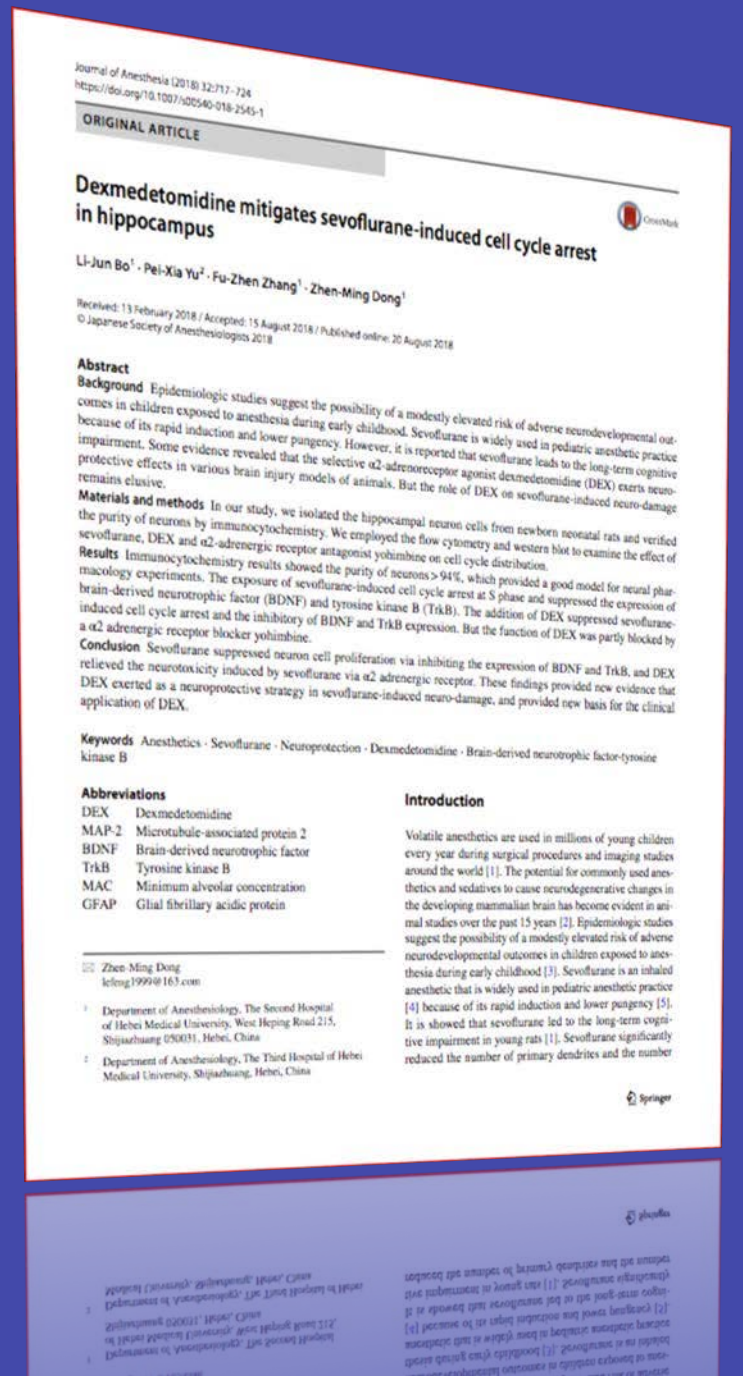
Editorial decision: January 2, 2018; **Accepted:** January 2, 2018

- 3β-OH: esteroide neuroactivo con propiedades analgésicas significativas
- 7 ratas recibieron 3β-OH, ketamina, o salino
  - 3β-OH es un hipnótico efectivo
  - Ketamina, pero no 3β-OH, causó neuroapoptosis
  - Ketamina, pero no 3β-OH, causó problemas en el aprendizage luego

Atluri N et al. Br J Anaesth. 2018 Apr;120(4):768-778.



Atluri N. Br J Anaesth. 2018 Apr;120(4):768-778.



Journal of Anesthesia (2018) 32:717–724
https://doi.org/10.1007/s00540-018-2545-1

ORIGINAL ARTICLE

Dexmedetomidine mitigates sevoflurane-induced cell cycle arrest in hippocampus

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Abstract

Background Epidemiologic studies suggest the possibility of a modestly elevated risk of adverse neurodevelopmental outcomes in children exposed to anesthesia during early childhood. Sevoflurane is widely used in pediatric anesthetic practice because of its rapid induction and lower pungency. However, it is reported that sevoflurane leads to the long-term cognitive impairment. Some evidence revealed that the selective α2-adrenoreceptor agonist dexmedetomidine (DEX) exerts neuroprotective effects in various brain injury models of animals. But the role of DEX on sevoflurane-induced neuro-damage remains elusive.

Materials and methods In our study, we isolated the hippocampal neuron cells from newborn neonatal rats and verified the purity of neurons by immunocytochemistry. We employed the flow cytometry and western blot to examine the effect of sevoflurane, DEX and α2-adrenergic receptor antagonist yohimbine on cell cycle distribution.

Results Immunocytochemistry results showed the purity of neurons > 94%, which provided a good model for neural pharmacology experiments. The exposure of sevoflurane-induced cell cycle arrest at S phase and suppressed the expression of brain-derived neurotrophic factor (BDNF) and tyrosine kinase B (TrkB). The addition of DEX suppressed sevoflurane-induced cell cycle arrest and the inhibitory of BDNF and TrkB expression. But the function of DEX was partly blocked by a α2 adrenergic receptor blocker yohimbine.

Conclusion Sevoflurane suppressed neuron cell proliferation via inhibiting the expression of BDNF and TrkB, and DEX relieved the neurotoxicity induced by sevoflurane via α2 adrenergic receptor. These findings provided new evidence that DEX exerted as a neuroprotective strategy in sevoflurane-induced neuro-damage, and provided new basis for the clinical application of DEX.

Keywords Anesthetics · Sevoflurane · Neuroprotection · Dexmedetomidine · Brain-derived neurotrophic factor-tyrosine kinase B

Abbreviations

DEX	Dexmedetomidine
MAP-2	Microtubule-associated protein 2
BDNF	Brain-derived neurotrophic factor
TrkB	Tyrosine kinase B
MAC	Minimum alveolar concentration
GFAP	Glial fibrillary acidic protein

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Introduction

Volatile anesthetics are used in millions of young children every year during surgical procedures and imaging studies around the world [1]. The potential for commonly used anesthetics and sedatives to cause neurodegenerative changes in the developing mammalian brain has become evident in animal studies over the past 15 years [2]. Epidemiologic studies suggest the possibility of a modestly elevated risk of adverse neurodevelopmental outcomes in children exposed to anesthesia during early childhood [3]. Sevoflurane is an inhaled anesthetic that is widely used in pediatric anesthetic practice [4] because of its rapid induction and lower pungency [5]. It is showed that sevoflurane led to the long-term cognitive impairment in young rats [1]. Sevoflurane significantly reduced the number of primary dendrites and the number

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- Cultivos de neuronas del hipocampo de ratas neonatales
- 4% sevo for 3, 6, or 12h
- Evaluación de ciclo celular por citometría
- Sevoflurano indujo paro de la fase S del ciclo celular
- Dexmedetomidina previno esto

Bo LJ et al. J Anesth. 2018 Oct;32(5):717-724.

Estudios Clínicos

Neuropsychological and Behavioral Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia

The Mayo Anesthesia Safety in Kids (MASK) Study

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ABSTRACT

Background: Few studies of how exposure of children to anesthesia may affect neurodevelopment employ comprehensive neuropsychological assessments. This study tested the hypothesis that exposure to multiple, but not single, procedures requiring anesthesia before age 3 yr is associated with adverse neurodevelopmental outcomes.

Methods: Unexposed, singly exposed, and multiply exposed children born in Olmsted County, Minnesota, from 1994 to 2007 were sampled using a propensity-guided approach and underwent neuropsychological testing at ages 8 to 12 or 15 to 20 yr. The primary outcome was the Full-Scale intelligence quotient standard score of the Wechsler Abbreviated Scale of Intelligence. Secondary outcomes included individual domains from a comprehensive neuropsychological assessment and parent reports.

Results: In total, 997 children completed testing (411, 380, and 206 unexposed, singly exposed, and multiply exposed, respectively). The primary outcome of intelligence quotient did not differ significantly according to exposure status; multiply exposed and singly exposed children scoring 1.3 points (95% CI, −3.8 to 1.2; $P = 0.32$) and 0.5 points (95% CI, −2.8 to 1.9; $P = 0.70$) lower than unexposed children, respectively. For secondary outcomes, processing speed and fine motor abilities were decreased in multiply but not singly exposed children; other domains did not differ. The parents of multiply exposed children reported increased problems related to executive function, behavior, and reading.

Conclusions: Anesthesia exposure before age 3 yr was not associated with deficits in the primary outcome of general intelligence. Although secondary outcomes must be interpreted cautiously, they suggest the hypothesis that multiple, but not single, exposures are associated with a pattern of changes in specific neuropsychological domains that is associated with behavioral and learning difficulties.

Visual Abstract: An online visual overview is available for this article at http://links.lww.com/ALN/B753. (ANESTHESIOLOGY 2018; 129:89-105)

DRUGS producing general anesthesia can cause neurodegeneration and long-term deficits in learning and behavior in young animals (including nonhuman primates).[1–5] Numerous studies have sought evidence for similar effects in children. Most observational studies find that multiple exposures to procedures requiring general anesthesia are associated with deficits in learning and behavior, albeit with small effect sizes in some studies.[6–10] Some, but not all, human studies also find an association between single exposures and a variety of outcomes.[8,9,11–18] These studies employed a wide range of designs and outcomes. Only two studies reported a comprehensive assessment of neuropsychological function: an unmatched cohort study[14] and another that carefully matched subjects who were and were not exposed to anesthesia, but included only children undergoing herniorrhaphy.

What We Already Know about This Topic

- There is strong evidence from preclinical studies that most general anesthetics modulate brain development. There is mixed evidence in humans that anesthesia exposure in early life is associated with changes in neurodevelopmental outcomes. The association may be stronger after multiple exposures.

What This Article Tells Us That Is New

- This matched cohort study found that anesthesia exposure before age 3 yr was not associated with deficits in the primary outcome of general intelligence.
- Single exposures were not associated with deficits in other neuropsychological domains (assessed as secondary outcomes). However, multiple exposures were found to be associated with modest decreases in processing speed and fine motor coordination. Parents also reported that multiply exposed children have more difficulties with behavior and reading.

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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Neuropsychological and Behavioral Outcomes in Children after Anesthesia Exposure

Matched cohort study, 1994 to 2007

Unexposed (411) Single exposure (380) Multiple exposures (206)

Exposure	Intelligence Quotient vs. Unexposed Children
Single	0.5 points lower (95% CI, −2.8 to 1.9; $P = 0.70$)
Multiple	1.3 points lower (95% CI, −3.8 to 1.2; $P = 0.32$)

Secondary Outcome: Processing speed and fine motor abilities were decreased in children with multiple exposures; there were no significant differences in attention, memory, executive function, expressive language, visual-motor abilities, or visual-spatial abilities between unexposed and either exposure category.

Secondary Outcome: Parents of children with multiple exposures reported more problems related to executive function, behavior, and reading (but not math); parents of children with a single exposure reported more problems related to executive function and reading.

Anesthesia before the age of 3 yr was not associated with deficits in general intelligence.

Warner DO *et al.* ANESTHESIOLOGY. July 2018.

ANESTHESIOLOGY

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Warner DO et al. Anesthesiology. 2018 Jul;129(1):89-105.

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RESEARCH REPORT

WILEY Pediatric Anesthesia

The impact of general anesthesia on child development and school performance: a population-based study

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Section Editor: Laszlo Vutskits

Summary

Background: There has been considerable interest in the possible adverse neurocognitive effects of exposure to general anesthesia and surgery in early childhood.
Aims: The aim of this data linkage study was to investigate developmental and school performance outcomes of children undergoing procedures requiring general anesthesia in early childhood.
Methods: We included children born in New South Wales, Australia of 37-weeks' gestation without major congenital anomalies or neurodevelopmental disability with either a school entry developmental assessment in 2009, 2012, or Grade-3 school test results in 2008-2014. We compared children exposed to general anesthesia aged <48 months to those without any hospitalization. Children with only 1 hospitalization with general anesthesia and no other hospitalization were assessed separately. Outcomes included being classified developmentally high risk at school entry and scoring below national minimum standard in school numeracy and reading tests.
Results: Of 211 978 children included, 82 156 had developmental assessment and 153 025 had school test results, with 12 848 (15.7%) and 25 032 (16.4%) exposed to general anesthesia, respectively. Children exposed to general anesthesia had 17%, 34%, and 23% increased odds of being developmentally high risk (adjusted odds ratio [aOR]: 1.17; 95% CI: 1.07-1.29); or scoring below the national minimum standard in numeracy (aOR: 1.34; 95% CI: 1.21-1.48) and reading (aOR: 1.23; 95% CI: 1.12-1.36), respectively. Although the risk for being developmentally high risk and poor reading attenuated for children with only 1 hospitalization and exposure to general anesthesia, the association with poor numeracy results remained.
Conclusion: Children exposed to general anesthesia before 4 years have poorer development at school entry and school performance. While the association among children with 1 hospitalization with 1 general anesthesia and no other hospitalization was attenuated, poor numeracy outcome remained. Further investigation of the specific effects of general anesthesia and the impact of the underlying health conditions that promot the need for surgery or diagnostic procedures is required.

- Niños expuestos a anestesia general antes de los 4 años
  - Pobre desarrollo escolar
- Al restringir a una sola hospitalización y una sola anestesia general:
  - Desarrollo escolar normal

Schneuer FJ. Paediatr Anaesth. 2018 Jun;28(6):528-536.

Resumen

- Aviso de la FDA
- Mayormente estudios pre-clínicos en ratas
- Múltiples anestésicos asociados a una incidencia baja de trastornos de aprendizaje pero…
- Co-factores???

Resumen

- Evidencia significativa que un solo anestésico de corta duración no está asociado a ningún riesgo a largo plazo en humanos
- Técnicas neuroprotectoras…

Gracias