COADYUVANTES PARA BLOQUEOS NEUROAXIALES EN NIÑOS

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SERVICIO ANESTESIOLOGIA-REANIMACION PEDIATRICA

UNIDAD DE DOLOR PEDIATRICO

SARTD-CHGUV Sesión de Formación Continuada
Valencia 13 de Noviembre de 2017

BLOQUEOS NEUROAXIALES EN PEDIATRIA

- Estabilidad hemodinámica
- Disminución en los requerimientos de anestesia general
- Control de la respuesta neuroendocrina al estrés quirúrgico
- Modulación de la la respuesta inflamatoria
- Recuperación de la función gastrointestinal
- Menor dependencia de ventilación mecánica postoperatoria. Ex-prematuros.
- Prevención de cuadros de dolor crónico postquirúrgico
- Analgesia postoperatoria
- Seguridad (0.12-0.85% morbilidad ¡Cuidado < 1 año!)

Pediatr. Anaesth. 2007 (17): 520-533
Pediatr. Anaesth. 2010(20):1061-69
Pediatr. Anaesth. 2012 (22) 10-18
Rev. Esp. Anesth. Reanim. 2016; 63(2):91-100

ANESTESICOS LOCALES

INTRADURAL	EPIDURAL		
	CAUDAL	TORACICA/LUMBAR	CONTINUA
Bupivacaína L-bupivacaína Tetracaína	Bupivacaína0.25% L-bupivacaína 0.25% Ropivacaína 0.2%	Bupivacaína L-bupivacaína Ropivacaína	Bupivacaína L-bupivacaína Ropivacaína Cloroprocaína
RN y Lactantes 1 mg/kg	Fórmula de Armitage	0.3-0.5 ml/kg bolo inicial	<3 meses 0.2mg/kg/h
>1 año 0.5 mg/kg	Dosis Máxima 2-2.5 mg/kg	Dosis Máxima 1.7 mg/kg	3meses-1 año 0.3mg/kg/h
			>1 año 0.4mg/kg/h

ESRA- ASRA. Curr Opin Anesthesiol 2017,30:613-620

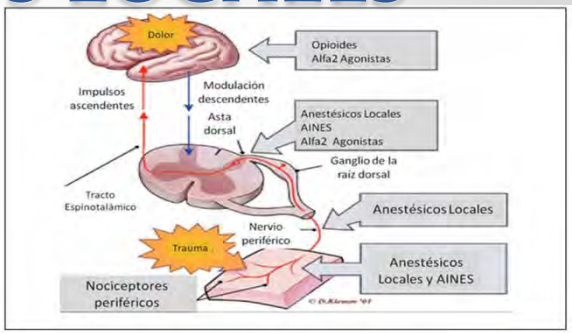
COADYUVAR

1. intr. Contribuir o ayudar a que algo se realice o tenga lugar.

Coadyuvantes: sustancias que contribuyen a la acción de un fármaco principal

COADYUVANTES Y ANESTESICOS LOCALES

contribuyen a:



Tomado de Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. AnesthAnalg 1993; 77:1049.
Figura 4. Las vías del dolor y las intervenciones que pueden modular la actividad en cada punto.

EFECTO
- AUMENTAR LA DURACION

MULTI
- POTENCIAR EL EFECTO

MODAL
- EVITAR EFECTOS SECUNDARIOS

- ¿1º ? COADYUVANTE EN BLOQUEO NEUROAXIAL EN PEDIATRIA

- Bloqueo intradural: ESTOVAINA + ESTRICNINA

  T1-T2 cirugía craneofacial, cervical o torácica
  T12-L1 laparotomías

  15 niños <10 años 1 caso de fisura palatina

- Estricnina (*Strychna nux vomica*) a bajas dosis es estimulante del SNC y podría haber mejorado la tolerancia a un bloqueo espinal alto

THOMAS JONNESCO
1860-1926 Rumanía

Pediatr Anaesth. 21 (2011) 1281

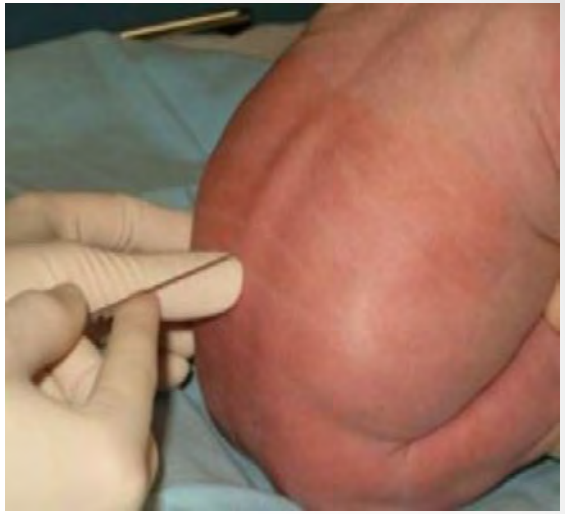
MECANISMO DE ACCION

- **Receptores medulares**
- **Sistémico?**

¿DE QUE EVIDENCIA DISPONEMOS?

- ✓INTRADURAL
- ✓EPIDURAL CONTINUA
- ✓CAUDAL EN DOSIS UNICA

INTRADURAL



- ✓ POCO UTILIZADA EN PEDIATRIA
- ✓ EXPREMATUROS CON ALTO RIESGO DE APNEA
- ✓ CIRUGIA <60-75 MINUTOS
- ✓ PROLONGAR LA DURACION DEL BLOQUEO CON COADYUVANTES ….

Pediatr Anesth. 22, 2012: 56-64

Spinal anesthesia in children: A review

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J Anaesthesiol Clin Pharmacol 2014; 30:10-18

Table 4: Additives used for spinal anesthesia in children

Additive (μg/kg)	Author	LA	Results
Epinephrine (2-3)	Abajian[6] 1984	Tetracaine	Prolonged from 84 (7.2) to 109 (5.3) min [N,I]
	Rice[43] 1994	Tetracaine	Prolonged from 86 (4) to 128 (3.3) min [I]
	Fosel[44] 1994	Bupivacaine	Prolonged from 50 to 95 min [I]
	Gupta[22] 2006	Bupivacaine	Mean duration of block 84±8 min [C]
Morphine (4-15)	Ganesh[45] 2008	No LA	Various surgeries (4-5 μ/kg): prolonged post-operative analgesia, no respiratory side-effects [C]
	Finkel[46] 1997	Tetracaine	Cardiac surgeries: 10 μg/kg hemodynamic stability with 24 hr analgesia (patients extubated in OR) [I,C]
	EschertzHuber[47] 2008	No LA	Scoliosis surgery (15 μ/kg): Decreased blood loss, safe and prolonged analgesia [C]
Fentanyl (0.2-2)	Piral[48] 2002	No LA	Cardiac surgery (2 μ/kg): Prolonged analgesia with cardio-respiratory stability [C]
	Batra[49] 2008	Bupivacaine	Lower abdominal and urologic surgery: 1 μg/kg, prolonged SA 74(6) vs. 51(5) mins. [I]
	Duman[50] 2010	Bupivacaine	Hernia repair: 0.2 μg/kg, lowered pain scores intraoperatively, ↑ post-operative analgesia (50 min) [C]
Clonidine (1-2)	Rochette[51] 2005	Bupivacaine	Inguinal hernia: 1 μg/kg: ↑ duration from 70 to 110 min. 2 μg/kg: more hypotension, sedation, and respiratory depression [N]
	Kaabachi[52] 2007	Bupivacaine	Orthopedic surgery (1 μg/kg): ↑ duration from 110 to 135 minutes and analgesia from 330 to 460 min [C]
	Cao[53] 2011	Bupivacaine	Orthopedic surgery (1 μg/kg): ↑ motor and sensory block, reduced propofol requirement [C]
Neostigmine (0.75)	Batra[54] 2009	Bupivacaine	Lower abdominal surgery: Significant prolongation, no increase in emesis or delayed recovery [I]

N = Neonates, I = Infants, C = Children

Clonidine Prolongs Spinal Anesthesia in Newborns: A Prospective Dose-Ranging Study

Alain Rochette, MD*, Olivier Raux, MD*, Rachel Troncin, MD*, Christophe Dadure, MD*, Régis Verdier, MD†, and Xavier Capdevila, MD, PhD*

Departments of *Anesthesia and Intensive Care "A" and †Medical Statistics, Hôpital Lapeyronie, CHU de Montpellier, France

(Anesth Analg 2004;98:56–9)

- 1µgr/kg prolonga el bloqueo de 67 (58-82) a 110 (113-125) minutos
- 2µgr/kg más efectos secundarios pausas de apnea (cafeína) e hipotensión

Clonidine added to bupivacaine in neonatal spinal anesthesia: a prospective comparison in 124 preterm and term infants

ALAIN ROCHETTE MD*, RACHEL TRONCIN MD*, OLIVIER RAUX MD*, CHRISTOPHE DADURE MD*, JEAN-FRANÇOIS LUBRANO MD*, ERIC BARBOTTE MD† AND XAVIER CAPDEVILA MD PhD*

Pediatric Anesthesia 2005 **15**: 1072–1077

Number of cardiorespiratory events

	Apnea			*Desaturation*			*Bradycardia*		
	Preoperative	*Postoperative*	*P-value*	*Preoperative*	*Postoperative*	*P-value*	*Preoperative*	*Postoperative*	*P-value*
Preterm ($n = 67$)	4	15	0.011	4	1	0.18	0	6	0.014
Full term ($n = 57$)	2	11	0.003	0	0	–	1	1	1

Apnea, respiratory pause lasting 10 s or longer; desaturation, SpO_2 <95% while breathing room air; bradycardia, heart rate <100 $b \cdot min^{-1}$. Pre/postoperative comparisons: Mc Nemar test; comparisons between groups according to Pearson or Fischer's exact test, as appropriate, did not show statistical significance.

INTRADURAL Y COADYUVANTES

- **CLONIDINA** 1µ/kg parece prolongar la duración del bloqueo (30 mn.)y analgesia postoperatoria(120 mn.). Precaución en neonatos.
- **MORFINA** : analgesia prolongada hasta 24 h. Efectos secundarios significativos Rango: 4-15 µ/kg
- **FENTANILO:** menor prolongación de analgesia (24-50 mn) 0.2 µ/kg. (Hasta 2 µ/kg: precaución)
- **ADRENALINA** 2-5 µg/kg prolonga 50% la duración del bloqueo (bupi y tetracaína)

EPIDURAL CONTINUA

BLOQUEOS METAMERICOS CONTINUOS en:

- cirugía torácica abierta
- intrabdominal mayor
- Osteoarticular mayor

Inserción de catéter nos permite analgesia postoperatoria 72 horas

- DISMINUIR LA DOSIS DE AL
- POTENCIAR EL BLOQUEO ANALGESICO
- DISMINUIR EL BLOQUEO MOTOR

- Levobupivacaina, Ropivacaína
- Opiáceos
- Clonidina

- Evidencia escasa: pocos estudios, dispersión metodológica

Does the use of fentanyl in epidural solutions for postthoracotomy pain management in neonates affect surgical outcome?

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Journal of Pediatric Surgery (2005) 40, 1118–1121

Index words:
Congenital cystic adenomatoid malformation of the lung;
Epidural analgesia;
Surgical outcomes

Abstract
Background/Purpose: Continuous epidural analgesia is routinely used to manage pain in infants undergoing resection of a congenital cystic adenomatoid malformation (CCAM) of the lung. Our aim was to determine if there is a difference in the length of stay (LOS), supplemental analgesic requirements, pain control, and the incidence of adverse respiratory events in infants receiving the 2 standard epidural solutions commonly used: bupivacaine 0.1% and bupivacaine 0.1% with fentanyl 2 to 5 μg/mL.
Methods: We retrospectively reviewed the charts of infants who received epidural infusions containing bupivacaine 0.1% (n = 18) and bupivacaine 0.1% with fentanyl 2 to 5 μg/mL (n = 10) after CCAM resection during a 12-month period. LOS, rescue opioid, and nonopioid analgesic use, incidence of respiratory depression, and pain scores were recorded.
Results: The LOS in patients receiving fentanyl in their epidural solution was 1 day longer than those receiving plain bupivacaine (median 4 vs 3 days, respectively). Nonopioid analgesic and rescue opioid use was greater in patients who did not have fentanyl in their epidural solutions. Pain ratings were not significantly different. The incidence of respiratory depression was greater in patients receiving epidural infusions containing fentanyl (50% vs 17%, respectively).
Conclusion: The addition of fentanyl to epidural infusions of bupivacaine in infants undergoing thoracotomy for resection of CCAM may prolong recovery and increase the incidence of adverse respiratory events without providing a significant analgesic benefit.

- Retrospectivo. 28
- Bupi 0.1%, Bupi 0.1% +fentanilo 2-5 πg/ml
- 1 día más de estancia . Igual dolor con menos analgesia de rescate
- Más ES (DR 50%/17%)

Postoperative epidural analgesia in children after major orthopaedic surgery

A randomised study of the effect on PONV of two anaesthetic techniques: low and high dose i.v. fentanyl and epidural infusions with and without fentanyl

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Department of Anaesthesiology, Ullevaal University Hospital Ullevaal, Norway

Background: The study was performed in order to improve postoperative pain management in children after major orthopaedic surgery. Two different anaesthetic techniques (sevoflurane-low fentanyl and propofol-higher fentanyl) and two different epidural mixtures (bupivacaine 1.5 mg ml $^{-1}$ and adrenaline 2 μg ml $^{-1}$ compared with bupivacaine 1 mg ml $^{-1}$, adrenaline 2 μg ml $^{-1}$ and fentanyl 2 μg ml $^{-1}$) were investigated with regard to postoperative analgesia and side effects, primarily postoperative nausea and vomiting (PONV).
Methods: Forty-two children were randomised into one of three groups: sevoflurane anaesthesia and epidural solution with fentanyl (SBAF); sevoflurane anaesthesia and epidural solution without fentanyl (SBA); propofol anaesthesia and epidural solution without fentanyl (PBA).
Results: Including fentanyl in the epidural mixture resulted in excellent postoperative analgesia without any need of i.v. opioids. However, 7 out of 16 children were nauseated and needed antiemetic drugs. On average, a 55–75% higher dose of bupivacaine was necessary to assure adequate analgesia when an epidural mixture without fentanyl was used. In addition, significantly more children needed i.v. opioids. Under these conditions there was no significant difference in pain scoring between the groups. There was significantly less nausea and less use of antiemetic drugs in children having epidurals without fentanyl in the sevoflurane groups. The same tendency, although not significant, was observed in the whole material. Sevoflurane anaesthesia resulted in less PONV than propofol anaesthesia, probably due to the higher amount of intravenous fentanyl used with the latter. This difference was not significant due to the small number of children included. Incidence of pruritus related significantly to epidural fentanyl.
Conclusion: A satisfactory postoperative analgesia can be achieved with both epidural mixtures used in the study. Epidural fentanyl results in better analgesia, but significantly more PONV and greater use of antiemetic drugs. Omitting epidural fentanyl results in less PONV, but significantly less profound analgesia and a need for additional treatment with i.v. opioids, in addition to a 55–75% higher epidural bupivacaine infusion. Both epidural treatments result in high and similar patient satisfaction and no serious complications. The study could not show any significant difference between the effect of sevoflurane and propofol anaesthesia on PONV.

Received 25 March, accepted for publication 8 November 2000

Key words: Analgesia; epidural; pediatrics; postoperative; nausea; vomiting.

- Prospectivo
- Bupi 0.1%+adrenalina 2μ/ml+fentanilo 2μ/ml y Bupi0.15%+adrenalina 2μ/ml
- Menor demanda analgésica y más efectos secundarios: NV y prurito
- No diferencias en dolor

A Comparison of Epidural Bupivacaine-Fentanyl and Bupivacaine-Clonidine in Children Undergoing the Nuss Procedure

(Anesth Analg 2006;103:322-7)

Table 3. Incidence of Complications, Pain Scores, and Medical Interventions in the Three Study Groups

	Bupivacaine + clonidine (BC) (n = 15)	Bupivacaine + fentanyl (BF) (n = 13)	Bupivacaine + fentanyl + clonidine (BFC) (n = 11)
Vomiting			
# of patients	4 (27%)	9 (69%)*	5 (55%)*
# of episodes/patient	0.3 ± 0.6	2.1 ± 0.6	1.1 ± 0.4
Pruritus			
# of patients	0 (0%)	11 (85%)#	2 (54%)#
# of episodes/patient	0	1.8 ± 0.4	1 ± 0.2
Sedation			
# of patients	10 (67%)	10 (77%)	8 (73%)
Score	1 (0–2)	1 (0–3)	1 (0–2)
VAS score			
Recovery room	3.2 ± 2.6	2.3 ± 2.3	3.5 ± 3.4
Study period	3.5 ± 1.6	2.9 ± 1.4	3.2 ± 1.5
PCEA demand dose (mL/patient)	22 ± 15	22 ± 17	22 ±1 6
Doses of nalbuphine	1.5 (0–6)	1 (0–6)	1 (0–3)

Values are number (%), median (range), or mean ± SD. The incidence of vomiting was significantly higher in the BF and BFC compared with the BC group (P = 0.03). The number of episodes of vomiting per patient was significantly higher in both BF and BFC groups compared with the BC group (P < 0.001). The incidence of pruritus was significantly higher in the BF and BFC groups compared with the BC group (P = 0.01). VAS = visual analog scale; PCEA = patient-controlled epidural analgesia

The Dose-Response Relationship for Clonidine Added to a Postoperative Continuous Epidural Infusion of Ropivacaine in Children

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*Department of Anesthesia and Intensive Care, IRCCS H "Casa Sollievo della Sofferenza" S. Giovanni Rotondo (FG), Italy; †Department of Anesthesia and Intensive Care, Regina Margherita Children's Hospital, Turin, Italy; and ‡Department of Paediatric Anaesthesia and Intensive Care, Astrid Lindgrens Children's Hospital, Karolinska Hospital, Stockholm, Sweden

Epidurally administered clonidine enhances the quality and duration of postoperative analgesia when it is used as an adjunct to local anesthetics in children. We investigated the dose-response relationship for epidural clonidine when added to a continuous postoperative epidural infusion of ropivacaine. By use of an observer-blinded design, 55 pediatric patients (1–4 yr old) were randomly given a postoperative epidural infusion of plain ropivacaine 0.1% 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ (Group R), ropivacaine 0.08% 0.16 $mg \cdot kg^{-1} \cdot h^{-1}$ plus clonidine 0.04 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (Group RC1), ropivacaine 0.08% 0.16 $mg \cdot kg^{-1} \cdot h^{-1}$ plus clonidine 0.08 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (Group RC2), or ropivacaine 0.08% 0.16 $mg \cdot kg^{-1} \cdot h^{-1}$ plus clonidine 0.12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (Group RC3). A clear dose-response relationship could be identified for a continuous infusion of epidural clonidine, with clonidine dosages in the 0.08–0.12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ range providing improved postoperative analgesia (reduced Children's Hospital of Eastern Ontario pain score, increased time to first supplemental analgesic demand, and a reduced total number of doses of supplemental analgesics during the first 48 h after surgery). Analgesia was improved without any signs of increased sedation or other side effects. The adjunct use of epidural clonidine in the dosage range of 0.08–0.12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ appears effective and safe for use in children.

(Anesth Analg 2001;93:71–6)

Clonidina epidural 0.08-0.12 µg/kg/h

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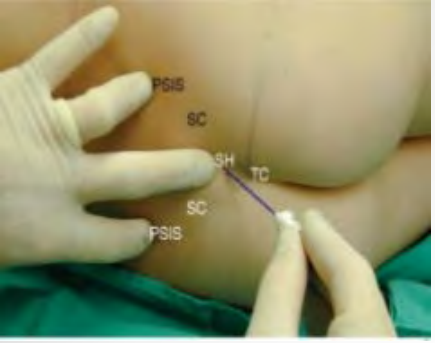
EPIDURAL CONTINUA Y COADYUVANTES

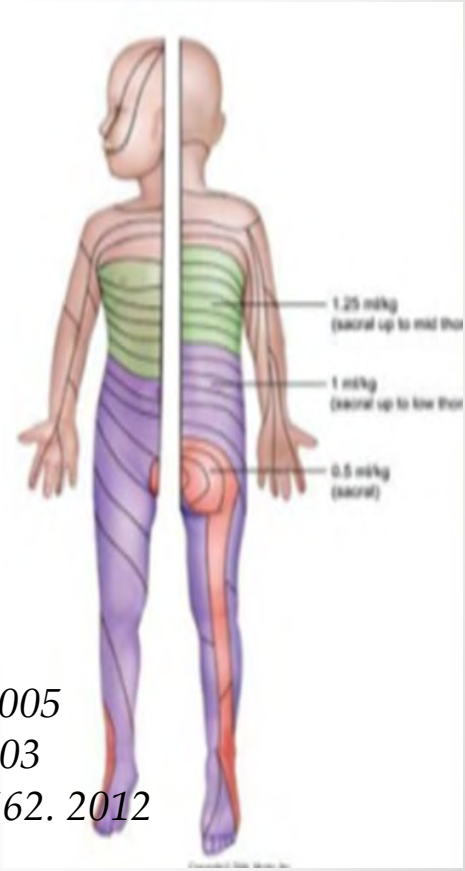
- **CLONIDINA** 0.08-0.12 μg/kg/h en bloqueo segmentario
- **FENTANILO** valorar menor dosis de AL frente a efectos secundarios
- **MORFINA** en bloqueo no segmentario frente a efectos secundarios



CAUDAL

- EL MAS UTILIZADO EN DOSIS UNICA
- EXCELENTE RELACION RIESGO-BENEFICIO
- BAJA CURVA DE APRENDIZAJE
- UTIL EN PACIENTES AMBULATORIOS

- ANALGESIA LIMITADA (4-6 H)



➢ COADYUVANTES OPIACEOS:

- MORFINA: riesgo de DR en lactantes . NV 30% RU: 6-30%
- FENTANILO: no evidencia. *Curr. Opini Anesthesiol 2016,29:626-31*
- Hidromorfona, Sufentanilo, Alfentanilo, Diamorfina, Butorfanol,Tramadol, Buprenorfina
- Relación riesgo-beneficio

➢ COADYUVANTES NO OPIACEOS

Br J Anesth 95(4):431-3. 2005
Br J Anaesth 90:487-98.2003
Anesth Analg 115(3)638-662. 2012

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Paediatric Anaesthesia 2003 **13**: 561–573

Review article

Nonopioid additives to local anaesthetics for caudal blockade in children: a systematic review

MARK ANSERMINO MBBCH FFA*, RAHUL BASU MD FRCA†,
CHRISTINE VANDEBEEK MBA* AND CAROLYNE

Conclusion: The evidence examined shows an increased duration of analgesia with clonidine, ketamine and midazolam. However, we are not convinced that the routine use of these adjuvants in the setting of elective outpatient surgery shows improved patient outcome. It is unclear if the potential for neurotoxicity is outweighed by clinical benefits. Further testing, including large clinical trials, is required before recommending routine use of nonopioid additives for caudal blockade in children.

British Journal of Anaesthesia 107 (4): 601–11 (2011)
Advance Access publication 16 August 2011 · doi:10.1093/bja/aer258

BJA

PAIN

Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials†

A. Schnabel[1], D. M. Poepping[1], P. Kranke[2], P. K. Zahn[3] and E. M. Pogatzki-Zahn[1*]

Study or subgroup	Ketamine +LA Mean	SD	Total	LA Mean	SD	Total	Weight	Mean difference i.v, fixed, 95% CI
Akbas and colleagues[18]	10	4.32	25	4	3.23	25	0.5%	6.00 (3.89, 8.11)
Akbas and colleagues[19] (B)	10	4.3	20	5	3.2	20	0.4%	5.00 (2.65, 7.35)
Akbas and colleagues[19] (R)	10	4	20	5	3.1	20	0.5%	5.00 (2.78, 7.22)
Choudhuri and colleagues[20]	9.2	3.9	25	6.5	4.1	25	0.5%	2.70 (0.48, 4.92)
De Negri and colleagues[22]	11.7	0.6	19	4.85	0.5	19	19.6%	6.85 (6.50, 7.20)
Kumar and colleagues[23]	11.6	4.4	20	7.6	5.2	20	0.3%	4.00 (1.01, 6.99)
Lee and Sanders[28]	12	12.6	16	3	3	16	0.1%	9.00 (2.65, 15.35)
Pan and Rudra[26]	9.8	2.1	20	6.7	2.1	20	1.4%	3.10 (1.80, 4.40)
Siddiqui and Chowdhury[29]	12.04	3.31	20	3.26	2.05	20	0.8%	8.78 (7.07, 10.49)
Somasundaran and Garasia[30]	9.32	0.45	33	4	0.27	34	75.9%	5.32 (5.14, 5.50)
Total (95% CI)			218			219	100.0%	5.60 (5.45, 5.76)

Heterogeneity: $\chi^2 = 95.09$, df = 9 ($P < 0.00001$); $I^2 = 91\%$

Mean difference i.v, fixed, 95% CI

Conclusions. Caudally administered ketamine, in addition to a local anaesthetic, provides prolonged postoperative analgesia with few adverse effects compared with local anaesthetics alone. There is a clear benefit of caudal ketamine, but the uncertainties about neurotoxicity relating to the dose of ketamine, single vs repeated doses and the child's age, still need to be clarified for use in clinical practice.

Efficacy and safety of clonidine as additive for caudal regional anesthesia: a quantitative systematic review of randomized controlled trials

Alexander Schnabel[1], Daniel M. Poepping[1], Esther M. Pogatzki-Zahn[1] & Peter K. Zahn[2]

Pediatric Anesthesia 21 (2011) 1219–1230

Study or Subgroup	Clonidine + LA Mean	SD	Total	LA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akbas 2005 (14)	14	3.1	25	4	3.23	25	8.9%	10.00 [8.25, 11.75]
Akin 2010 (31)	8	1.72	20	5.2	2.55	20	9.7%	2.80 [1.45, 4.15]
Bajwa 2010 (30)	13.4	3.4	22	8.5	3.4	22	8.3%	4.90 [2.89, 6.91]
Constant 1998 (15)	4.3	2	16	2.7	0.5	14	10.3%	1.60 [0.59, 2.61]
De Negri 2001 (18)	8.2	0.38	20	4.85	0.5	19	11.1%	3.35 [3.07, 3.63]
Ivani 1996 (20)	3.6	2.9	21	2.4	0.9	21	9.8%	1.20 [−0.10, 2.50]
Jamali 1994 (21)	16.45	9.55	15	7.66	7.32	15	2.7%	8.79 [2.70, 14.88]
Koul 2009 (32)	10.25	6.03	20	4.5	0.87	20	7.0%	5.75 [3.08, 8.42]
Lee 1994 (24)	9.8	2.1	23	5.2	1.2	23	10.3%	4.60 [3.61, 5.59]
Motsch 1997 (25)	20.9	7.4	20	14.4	10.9	20	2.9%	6.50 [0.73, 12.27]
Oner 2000 (33)	15.1	7.3	20	9.53	6.8	20	4.3%	5.57 [1.20, 9.94]
Sharpe 2001 (26)	6.36	3.34	25	4.67	2.86	25	8.9%	1.69 [−0.03, 3.41]
Wheeler 2005 (29)	8.68	4.35	15	7.45	5	15	5.7%	1.23 [−2.12, 4.58]
Total (95% CI)			**262**			**259**	**100.0%**	**3.98 [2.84, 5.13]**

Heterogeneity: $Tau^2 = 3.05$; $Chi^2 = 99.54$, df = 12 ($P < 0.00001$); $I^2 = 88\%$

Test for overall effect: $Z = 6.82$ ($P < 0.00001$)

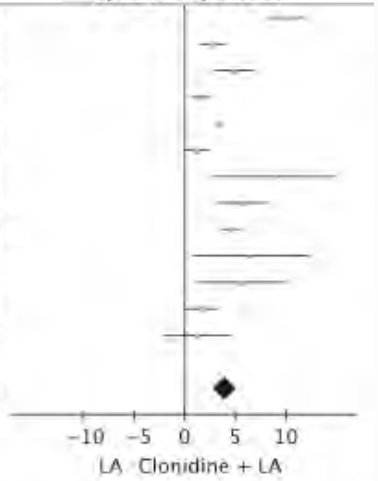


Figure 2 Pooled data analysis assessing the duration of postoperative analgesia (hours) ('time until first rescue requirement').

- 20 ensayos aleatorizados ; 993 . Niños 2-6 años
- CLONIDINA1-2µg/kg +AL frente a AL
- Mayor duración de analgesia postoperatoria 3.98 h;(95% IC:2.84-5-13 p<0.00001)
- Menor analgesia de rescate RR 0.72; (95%; IC: 0.57-0.90 p=0.003
- Efectos secundarios no e.s.: prolongación de bloqueo motor, sedación moderada, hipotensión

Paediatric Anaesthesia 2002 **12**: 637–640

Case report

Apnoea in a former preterm infant after caudal bupivacaine with clonidine for inguinal herniorrhaphy

CLAUDIA FELLMANN, ANDREAS C. GERBER AND MARKUS WEISS

Department of Anaesthesia, University Children's Hospital, Zurich, Switzerland

Paediatric Anaesthesia 1999 **9**: 81–83

Case report

Can a dose of 2 μg·kg^{-1} caudal clonidine cause respiratory depression in neonates?

CHRISTIAN BRESCHAN MD, DEAA*, RUTH KRUMPHOLZ MD*, RUDOLF LIKAR MD*, RAIMUND KRASCHL MD† AND HANNES V. SCHALK MD*

**Department of Anaesthesia, LKH Klagenfurt, Austria, †Department of Paediatrics Neonatal Intensive Care Unit, LKH Klagenfurt, Austria*

Clonidine in Preterm-Infant Caudal Anesthesia May Be Responsible for Postoperative Apnea

Jean-Christophe Bouchut, M.D., Rémi Dubois, M.D., and Jean Godard, M.D.

Regional Anesthesia and Pain Medicine, Vol 26, No 1 (January–February), 2001: pp 83–85

Clonidina 1.25-2 μgr/kg

Valencia 13 de Noviembre de 2017

Analgesic effect and adverse events of dexmedetomidine as additive for pediatric caudal anesthesia: a meta-analysis

Yao Tong[1,2], Hao Ren[1], Xibing Ding[1,2], Shuqing Jin[1,2], Zhixia Chen[2] & Quan Li[1,2]

Pediatric Anesthesia 24 (2014) 1224–1230

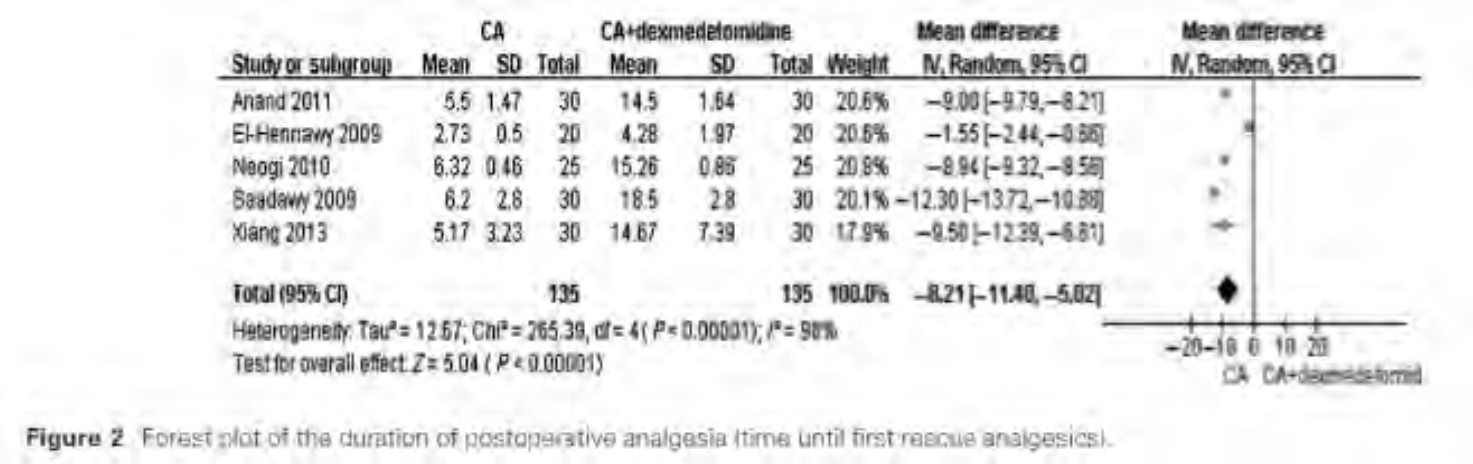
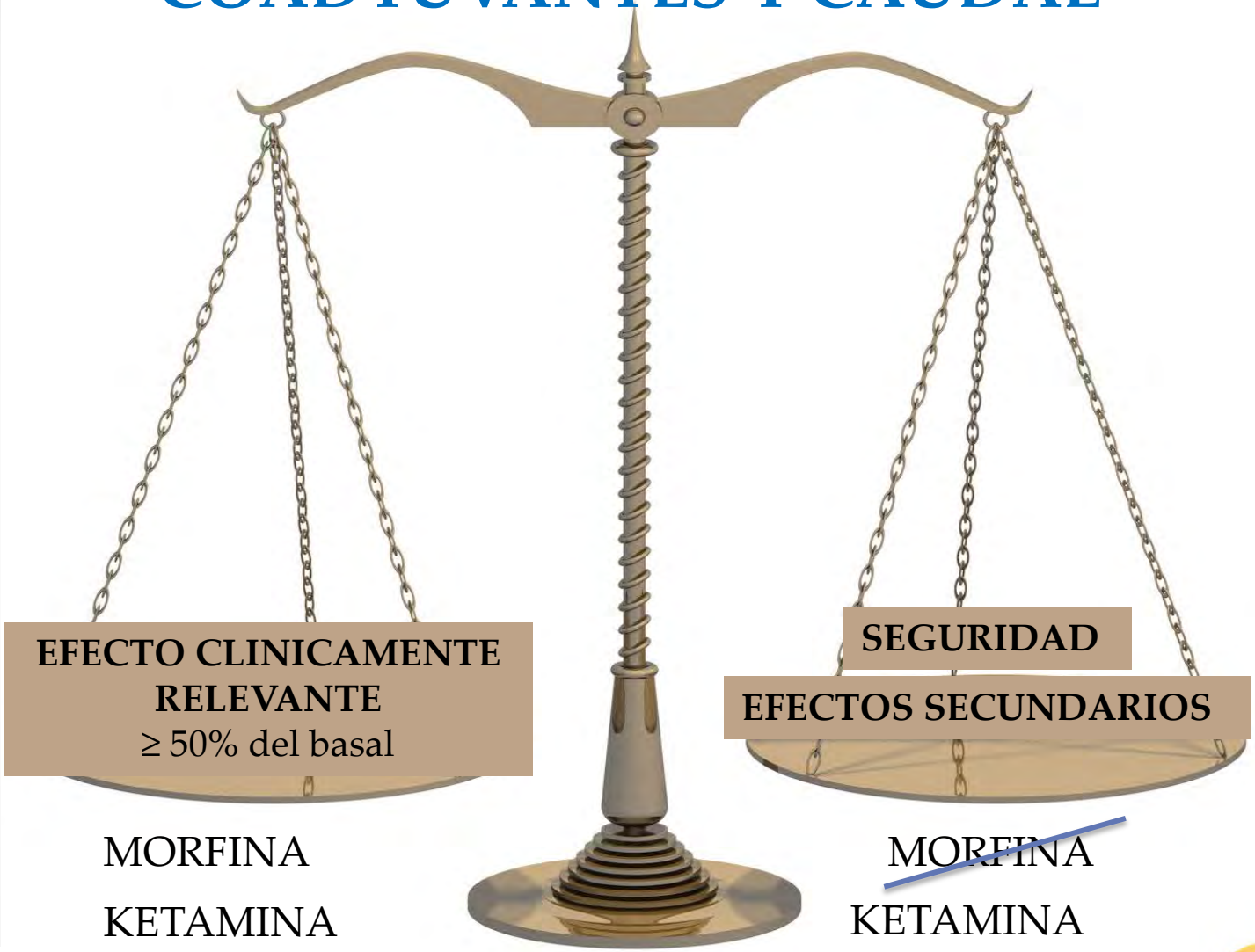


Figure 2 Forest plot of the duration of postoperative analgesia (time until first rescue analgesics).

- 6 RCTs 328 niños 1-6 años.
- Dexmedetomidina 1-2 µg/kg+AL frente a AL (Ropi y Bupivacaína)
- Mayor efecto analgésico 8.21 h; (95%: IC:11.40-5.02, p<0.00001). No diferencias entre dosis
- No ES signficativos . Bradicardia en 1 estudio con 2µg/kg

COADYUVANTES Y CAUDAL



EFECTO CLINICAMENTE RELEVANTE
≥ 50% del basal

MORFINA

KETAMINA

CLONIDINA

DEXMEDETOMIDINA

SEGURIDAD

EFECTOS SECUNDARIOS

~~MORFINA~~

KETAMINA

CLONIDINA

DEXMEDETOMIDINA

SEGURIDAD y COADYUVANTES

- ✓ **SIN PRESERVANTES O ESTABILIZANTES**
- ✓ **SIN NEUROTOXICIDAD DIRECTA**
- ✓ **SIN EFECTO NEURODEGENERATIVO. APOPTOSIS**

Curr Opin Anesthesiol 2016,29:626-631
Pediatr Anesth 2015 25:100-6

SARTD-CHGUV Sesión de Formación Continuada
Valencia 13 de Noviembre de 2017

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

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

≤ 3 AÑOS
≥ 3 HORAS
≥ 3 ANESTESIAS

Safety Announcement

[12-14-2016] The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains.

List of General Anesthetic and Sedation Drugs Affected by this Label Change*

Generic Name	Brand Name
desflurane	Suprane
etomidate	Amidate
halothane	Only generic is available
isoflurane	Forane
ketamine	Ketalar
lorazepam injection	Ativan
methohexital	Brevital
midazolam injection, syrup	Only generic is available
pentobarbital	Nembutal
propofol	Diprivan
sevoflurane	Ultane, Sojourn

*This list includes anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity. No specific medications have been shown to be safer than any other.

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communication

FDA approves label changes for use of general anesthetic and sedation drugs in young children

This is an update to the FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women issued on December 14, 2016.

Safety Announcement

[4-27-2017] The U.S. Food and Drug Administration (FDA) is notifying the public that we have approved previously announced label changes regarding the use of general anesthetic and sedation medicines in children younger than 3 years. These changes include:

- A new Warning stating that exposure to these medicines for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years.
- Addition of information to the sections of the labels about pregnancy and pediatric use to describe studies in young animals and pregnant animals that showed exposure to general anesthetic and sedation drugs for more than 3 hours can cause widespread loss of nerve cells in the developing brain; and studies in young animals suggested these changes resulted in long-term negative effects on the animals' behavior or learning.

MORFINA

0.1%

- Efecto analgésico significativo (24h)

1%

- Efectos secundarios significativos

- Cloruro sódico, agua
- Etiquetado para uso epidural e intratecal

Validation of a Preclinical Spinal Safety Model

Effects of Intrathecal Morphine in the Neonatal Rat

B. David Westin, M.D.,* Suellen M. Walker, M.B.B.S., Ph.D., F.A.N.Z.C.A.,† Ronald Deumens, Ph.D.,‡ Marjorie Grafe, M.D., Ph.D.,§ Tony L. Yaksh, Ph.D.‖

- In rats, the therapeutic to toxic ratio of spinal morphine was 300 when given 3 days after birth, and at least 20 when given 3 weeks after birth
- Assessing safety of spinal drugs in rat pups is possible, and morphine is not more toxic in newborn than in adolescent rats

Anesthesiology 2010; 113:185–99

FENTANILO

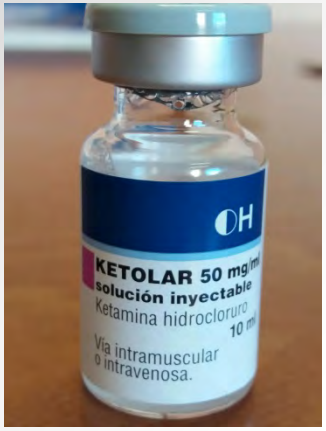
50µg/ml

- Efecto analgésico no significativo

- Efectos secundarios significativos

- Cloruro sódico, agua
- Off-label

KETAMINA



50mg/ml

- Efecto analgésico significativo (5-6h)

- Pocos efectos secundarios

- Excipiente: Cloruro de bencetonio
- S-ketamina sin excipientes
- Off-label

  Neuroapoptosis y daño glial

Effects of Intrathecal Ketamine in the Neonatal Rat

Evaluation of Apoptosis and Long-term Functional Outcome

Suellen M. Walker, M.B.B.S., Ph.D., F.A.N.Z.C.A.,* B. David Westin, M.D.,†
Ronald Deumens, Ph.D.,‡ Marjorie Grafe, M.D., Ph.D.,§ Tony L. Yaksh, Ph.D.‖

What This Article Tells Us That Is New

- In 3-day-old rat pups, spinal ketamine reversed hypersensitivity from peripheral inflammation
- At the antihypersensitivity dose, ketamine also produced spinal cord histologic toxicity and prolonged gait disturbances

Anesthesiology 2010; 113:147-59

CLONIDINA

150 microgr/ml

- Efecto analgésico significativo (4h)

- Efectos secundarios aceptables ? <1año?

- Acido clorhídrico, cloruro sódico y agua
- Off-label

- No neuroapoptosis

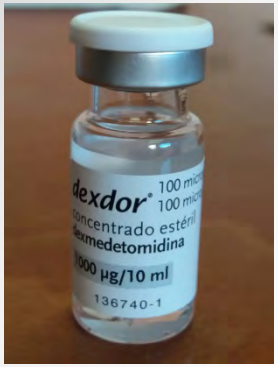
Intrathecal Clonidine in the Neonatal Rat: Dose-Dependent Analgesia and Evaluation of Spinal Apoptosis and Toxicity

Suellen M. Walker, MBBS, PhD, FANZCA, FFPMANZCA,* Marjorie Grafe, MD, PhD,† and Tony L. Yaksh, PhD†

CONCLUSIONS: Intrathecal clonidine in the postnatal rat did not produce signs of spinal cord toxicity, even at doses much larger than required for analgesia. The therapeutic ratio (maximum tolerated dose/antihyperalgesic dose) was >300 at P3, >30 at P7, and >10 at P21. These

(Anesth Analg 2012;115:450–60)

DEXMEDETOMIDINA



100 µgr/ml

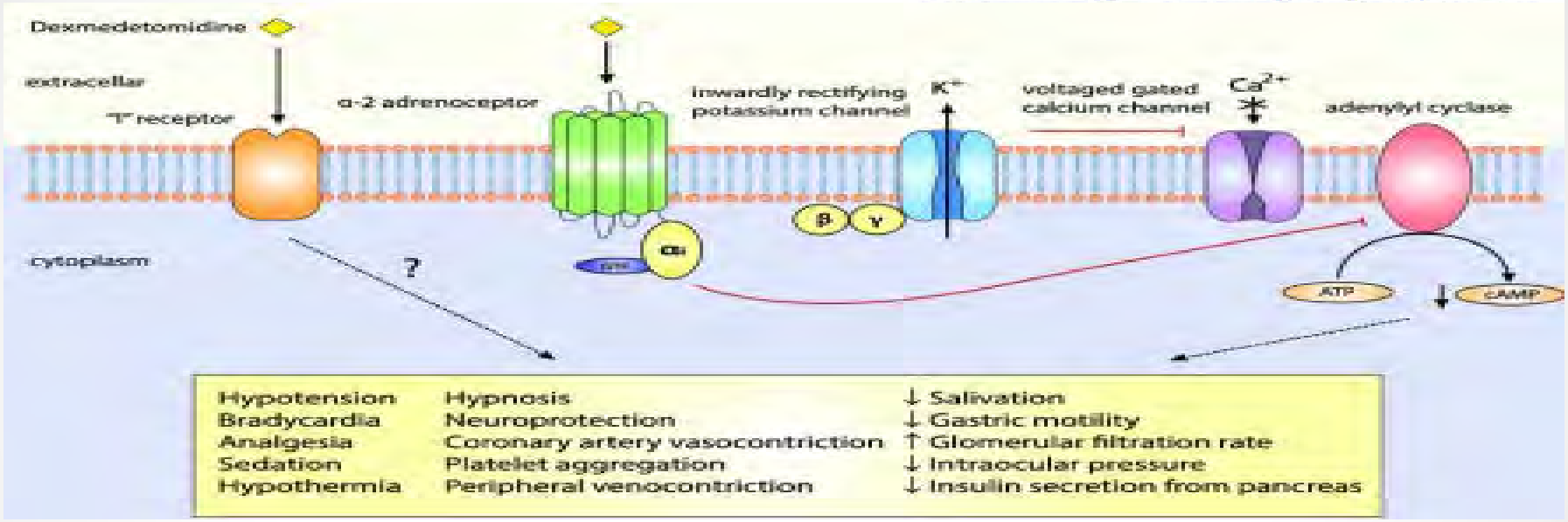
- Efecto analgésico significativo (8h)
- Efectos secundarios tratables
- Neurotoxicidad??
- Cloruro de sodio y agua
- off-label

Neuroprotection and neurotoxicity in the developing brain: an update on the effects of dexmedetomidine and xenon

Azeem Alam [a], Ka Chun Suen [a], Zac Hana [a], Robert D. Sanders [b], Mervyn Maze [c], Daqing Ma [a,*]

[a] Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea & Westminster Hospital, London, UK
[b] Department of Anesthesiology, University of Wisconsin, Madison, WI, USA
[c] Department of Anesthesia and Perioperative Care, University California San Francisco, CA, USA

Neurotoxicology and Teratology 60 (2017) 102–116



- Neuroprotección
  - Frente a agentes anestésicos neurotóxicos: isofluorane, sevofluorane *(Br J Anaesth 2017 Sep1;119(3):506-516)*
  - Daño hipóxico-isquémico
  - Mejores resultados en asfixia perinatal
- Neuroapoptosis a altas dosis

The efficacy and neurotoxicity of dexmedetomidine administered via the epidural route

S. Konakci*, T. Adanir*, G. Yilmaz*, T. Rezanko†

*Ataturk Training and Research Hospital, Departments of *Anaesthesiology, †Pathology, Izmir, Turkey*

European Journal of Anaesthesiology 2008; 25: 403–409

[22]. As dexmedetomidine has neuroprotective effects, it could be expected that dexmedetomidine by epidural or intrathecal administration would not be harmful. However, this study has shown that dexmedetomidine (10 μg) produced the moderate or severe demyelinization of myelin sheaths in the white matter, when it was administered via the epidural route. This effect could be related to vasoconstriction of the medullary spinal vessels [23] and pH of dexmedetomidine. Precedex (dexmedetomidine) is supplied as a clear, colourless, isotonic solution with a pH of 4.5–7.0, and this pH may cause demyelinization. Each 1 mL of Precedex contains 118 μg of dexmedetomidine HCl (equivalent to 100 μg dexmedetomidine base) and 9 mg of NaCl in water. The solution is preservative-free and contains no additives or chemical stabilizers. Thus, we do not think that demyelination could be related to additives or chemical stabilizers.

Neurotoxicity of intrathecal injections of dexmedetomidine into the rat spinal dorsal horn*

Jiabao Hou, Zhongyuan Xia, Xingpeng Xiao, Xing Wan, Bo Zhao

Department of Anesthesiology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China

Neural Regen Res. 2012;7(23):1765-1770.

Abstract

To investigate the neurotoxicity of intrathecal injections of dexmedetomidine, Sprague-Dawley rats were intrathecally injected with dexmedetomidine at doses of 0.75, 1.50 and 3.00 μg/kg into the spinal dorsal horn. We found that c-Fos expression in the rat spinal dorsal horn peaked at 7 hours following the 3.00 μg/kg dexmedetomidine injection, while the levels of c-Fos expression following 0.75 and 1.50 μg/kg dexmedetomidine were similar to those in the spinal dorsal horn of normal rats. At 48 hours following administration, the level of c-Fos expression was similar to normal levels. In addition, the intrathecal injections of dexmedetomidine increased paw withdrawal mechanical thresholds and prolonged thermal tail flick latencies. These results indicate that dexmedetomidine has pronounced antinociceptive effects. However, dexmedetomidine appears to have neurotoxic effects in the spinal cord because it increased c-Fos expression in the spinal dorsal horn within 7 hours following administration.

Jiabao Hou★, Master, Department of Anesthesiology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China

Corresponding author: Zhongyuan Xia, Ph.D., Professor, Department of Anesthesiology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China xiazhongyan2005@yahoo.com.cn


Right Decision
Wrong Decision

¿DISPONEMOS DE LA EVIDENCIA NECESARIA PARA ADMINISTRAR DE MANERA *RUTINARIA* COADYUVANTES EN BLOQUEOS NEUROAXIALES EN NIÑOS DE *CUALQUIER EDAD?*

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Valencia 13 de Noviembre de 2017

Adjuncts should always be used in pediatric regional anesthesia

Per-Arne Lönnqvist[1,2]

1 Paediatric Anaesthesia & Intensive Care, Section of Anaesthesiology & Intensive Care, Department of Physiology & Pharmacology, Karolinska Institutet, Stockholm, Sweden
2 Paediatric Anaesthesia, Inetsive Care & ECMO Services, Astrid Lindgrens Children's Hospital/Karolinska University Hospital-Solna, Stockholm, Sweden

Pediatric Anesthesia 25 (2015) 100–106

Table 1 Suggestions on how to use adjuncts in daily clinical practice when performing pediatric regional anesthesia. All adjuncts must be preservative-free

Type of block	Recommended adjuncts	Supporting references
Spinal block in expremature babies, neonates and infants	Clonidine 1 mcg·kg^{-1}	(28,61)
Caudal blocks in ex-premature babies, neonates and infants	Clonidine 1 mcg·kg^{-1} (Morphine 33–50 mcg·kg^{-1}, rarely indicated)	(8,9,13,60,61)
Caudal blocks for children >1 years of age	S-ketamine 0.5 mcg·kg^{-1} Clonidine 1–2 mcg·kg^{-1}	(12,13,23)
Continuous epidural analgesia with adequate segmental tip position	Clonidine >0.1 mcg·kg^{-1}·h^{-1}	(31)
Continuous epidural analgesia with suboptimal segmental tip position	Morphine 33–50 mcg·kg^{-1}, Intermittent injections 1–3 times daily	(8,9)
Peripheral nerve blocks, single injection	Clonidine 1–2 mcg·kg^{-1}	(35)
Peripheral nerve blocks, continuous infusion	Clonidine >0.1 mcg·kg^{-1}·h^{-1}	(extrapolated from 31)

Adjunct analgesic drugs to local anaesthetics for neuroaxial blocks in children

Märit Lundblad[a,b] *and Per-Arne Lönnqvist*[a,b]

Curr Opin Anesthesiol 2016, 29:626–631

- All adjuncts must be preservative-free and must have been shown to be without neurotoxic properties.
- Clonidine is the only adjunct that successfully can be used for both peripheral and neuroaxial blocks in children of all ages.
- Morphine and ketamine are effective as adjuncts to neuroaxial blockade in children if the proper limitations are taken into account.
- Dexmedetomidine appears as a new interesting adjunct in this context.
- All other adjuncts should be regarded as still experimental and should not be used outside clinical trials.

Table 1. Neuroaxial blocks in children – suggested adjuncts and doses

Spinal block (ex-premature babies – neonates)	Clonidine 1 $\mu g\,kg^{-1}$
Caudal block (ex-premature, neonate, infant)	Clonidine 1 $\mu g\,kg^{-1}$
Caudal block >1 year of age	S-ketamine 0.5 $\mu g\,kg^{-1}$; Clonidine 1–2 $\mu g\,kg^{-1}$ (special indications: morphine 33–50 $\mu g\,kg^{-1}$)
Continuous epidural block with acceptable catheter tip location	Clonidine >0.1 $\mu g\,kg^{-1}\,h^{-1}$
Continuous epidural block with suboptimal catheter tip location	Morphine 33–50 $\mu g\,kg^{-1}$ as intermittent injection 1–3 times per day

¿DISPONEMOS DE LA EVIDENCIA NECESARIA PARA ADMINISTRAR DE MANERA *RUTINARIA* COADYUVANTES EN BLOQUEOS NEUROAXIALES EN NIÑOS DE *CUALQUIER EDAD?*

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1. DE QUE DISPONGO?
2. QUE PACIENTE TENGO?
3. QUE ALTERNATIVAS PUEDO OFRECERLE?

SARTD-CHGUV Sesión de Formación Continuada
Valencia 13 de Noviembre de 2017

INTRADURAL:

MORFINA sin AL

EPIDURAL CONTINUA:

FENTANILO

CLONIDINA en dolor oncológico

CAUDAL dosis única:

NO COADYUVANTES

CLONIDINA SIN EXCIPIENTE
SABER MAS DE LA DEXMEDETOMIDINA

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Gracias