

NEURAXIAL DEXMEDETOMIDINE: HELP OR HYPE?

GREGORY COLLINS, DNP, CRNA

1

REVIEW	CONSIDER	PROPOSE
Review the pharmacokinetics/ pharmacodynamics of neuraxial dexmedetomidine	Consider the evidence regarding the safety and efficacy of neuraxial dexmedetomidine	Propose clinical avenues to incorporate neuraxial dexmedetomidine into practice

2

PHARMACOLOGY

- FDA APPROVED IN 1999
- SHORT-TERM SEDATION FOR INTUBATED, MECHANICALLY-VENTILATED PATIENT
- FDA EXPANDED INDICATIONS IN 2008
- PERIOPERATIVE AND PROCEDURAL SEDATION

3

PHARMACOLOGY

FDA-APPROVED ROUTES OF ADMINISTRATION

Intrathecal
Targeted delivery of the drug directly to the central spinal fluid.

4

PHARMACOLOGY

α_2 RECEPTOR

- CONCENTRATED IN BRAIN (PONS, MEDULLA) AND SPINAL CORD
- PRIMARILY PRESYNAPTIC
- RECEPTOR ACTIVATION REDUCES NEUROTRANSMITTER RELEASE

5

PHARMACOLOGY

DEXMEDETOMIDINE

- α RECEPTOR AGONIST/
1600x $\alpha_2 > \alpha_1$
- VERY LIPOPHILIC, RAPIDLY CROSSES MEMBRANES, BBB
- HEPATIC METABOLISM, "INACTIVE" METABOLITES

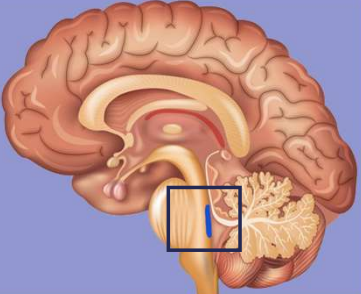
6

PHARMACOLOGY

LOCUS CERULEUS

RESPONSIBLE FOR VIGILANCE, AROUSAL

↓ NOREPINEPHRINE = SEDATION, HYPNOSIS



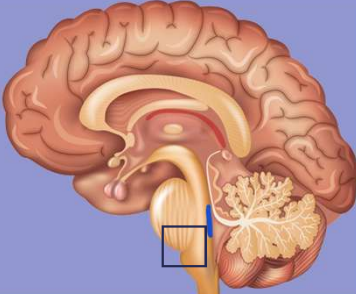
7

PHARMACOLOGY

R.V.M.

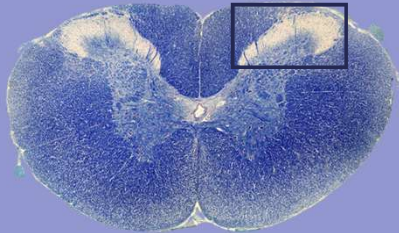
VASOMOTOR CENTER, CARDIAC/VASCULAR TONE

↓ NOREPINEPHRINE = ↓ HR, ↓ BP



8

PHARMACOLOGY




DORSAL HORN

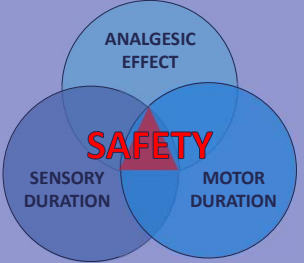
ASCENDING PAIN PATHWAYS / INTERNEURONS

↓ SUBSTANCE-P / GLUTAMATE = ↓ NOCICEPTIVE TRANSMISSION

9


EVIDENCE

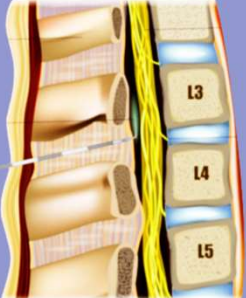




10

EVIDENCE





11

EVIDENCE

Review Article
Effect of Epidural Dexmedetomidine as an Adjuvant to Local Anesthetics for Labor Analgesia: A Meta-Analysis of Randomized Controlled Trials

9 STUDIES	COMPARED EPIDURAL DEXMEDETOMIDINE TO PLACEBO AND TO EPIDURAL OPIOIDS
DEXMEDETOMIDINE PROVIDED SUPERIOR PAIN SCORES AT VARIOUS TIME POINTS, INCLUDING AT TIME OF DELIVERY (P=0.0002)	
↓ INCIDENCE OF N/V (P=0.002), ↑ INCIDENCE OF ↓ MATERNAL HR (P=0.04)	

"Epidural dexmedetomidine has the potential to offer a better analgesic effect than placebo, similar labor pain control to opioids, and has no definite adverse effects on the parturient or fetus, but more high-quality studies are needed to confirm these conclusions."

12

EVIDENCE

Evaluation of the effect of dexmedetomidine combined with ropivacaine in epidural labor analgesia: a systematic review and meta-analysis

17 STUDIES COMPARED EPIDURAL BUP + DEXMEDETOMIDINE TO BUP + PLACEBO AND TO BUP + SUFENTANIL

DEXMEDETOMIDINE PROVIDED LOWER VAS SCORES AND INCREASED RAMSAY SEDATION SCORES

NO INCREASE IN MOTOR BLOCK, NO INCREASE IN NEONATAL ADVERSE EVENTS

"In patients with singleton full-term pregnancy, ropivacaine + dexmedetomidine have better analgesic and sedative effects than in the control group. Both groups have no significant motor block and neonatal asphyxia and hypoxia."

Zhou H, Wen L, Guo G, Zhao Y, Liu W. Evaluation of the effect of dexmedetomidine combined with ropivacaine in epidural labor analgesia: a systematic review and meta-analysis. *Int J Anesth Sedation.* 2019;2019:1-10. doi:10.1155/2019/1456760004

13

EVIDENCE

14

EVIDENCE

A Systematic Review and Meta-analysis of Efficacy and Safety of Dexmedetomidine Combined With Intrathecal Bupivacaine Compared to Placebo

21 STUDIES COMPARED INTRATHECAL DEXMEDETOMIDINE + BUP TO BUP + PLACEBO (+/- MULTIPLE CONTROLS)

↑ DURATION OF MOTOR BLOCK, SENSORY BLOCK, ANALGESIA

NO SIGNIFICANT DIFFERENCES IN N/V, ↓HR, ↓BP
↓ INCIDENCES OF PERIOPERATIVE SHIVERING

"Intrathecal dexmedetomidine when combined with bupivacaine was found to significantly increase the three efficacy parameters, i.e. duration of sensory block, motor block, and analgesia. It also appears to be safe with no increased risk of bradycardia or hypotension. It is also associated with decreased postoperative shivering."

Wang Y, Wu Y, Wang Z et al. Comparison of efficacy and safety of intrathecal dexmedetomidine combined with bupivacaine for cesarean section: a systematic review and meta-analysis. *Int J Anesth Sedation.* 2020;2020:1-10. doi:10.1155/2020/1456760004

15

EVIDENCE

Dexmedetomidine as an adjuvant for single spinal anesthesia in patients undergoing cesarean section: a system review and meta-analysis

9 STUDIES COMPARED BUPI + DEX TO BUPI + PLACEBO

↓ ONSET TIME FOR SENSORY AND MOTOR BLOCK

PROLONGED SENSORY/MOTOR BLOCK

↓ INCIDENCE OF SHIVERING

NO SIGNIFICANT DIFFERENCES IN APGARS

"The use of intrathecal dexmedetomidine during cesarean section can shorten the onset time of spinal anesthesia and enhance the effect of local anesthetic. It has no significant impact on neonates and there were no other adverse events."

Wen QH, Liu H, Zhou X, Zhao Y, Liu Y. Dexmedetomidine as an adjuvant for single spinal anesthesia during cesarean section: a systematic review and meta-analysis. *Int J Anesth Sedation.* 2020;2020:1-10. doi:10.1155/2020/1456760004

16

EVIDENCE

	Group Bv	Group BvF	Group BvD	P
Time of onset of sensory block, min	7.8	7.6	7.1	0.65
Highest sensory block level	T4 42%	T4 40%	T4 44%	0.27
Time to highest sensory block level, min	9.1 (3.52)	8.47 (2.18)	8.10 (3.55)†	0.041†
Time of onset of motor block, min	7.6 (2.20)	7.4 (2.80)	7.1 (2.25)	0.22
Regression time to T10, min	102.20 (16.15)	117.71 (21.36)	152.9 (39.62)	0.003 *
Duration of sensory block, min	155.26 (23.09)	179.0 (38.83)*	211.73 (51.88)	0.0025 *
Time for complete motor recovery, min	127.5 (25.71)	130.65 (29.87)	128.55 (28.90)	0.81
Onset of postoperative pain, min	220.55 (28.64)	265.72 (25.16)	352.45 (26.17)	0.001 *

Wang Y, Wu Y, Wang Z et al. Comparison of efficacy and safety of intrathecal dexmedetomidine combined with bupivacaine for cesarean section: a systematic review and meta-analysis. *Int J Anesth Sedation.* 2020;2020:1-10. doi:10.1155/2020/1456760004

17

PRACTICE

EPIDURAL DOSING

INFUSION / PCEA

0.25-0.5 mcg/ml

LOADING / BOLUS

0.1-1 mcg/kg

18

PRACTICE

TABLE 1. Demographics, labor characteristics, and neonatal outcomes of laboring patients.

	Fentanyl 2 µg/ml	Dexmedetomidine 0.3 µg/ml	Dexmedetomidine 0.4 µg/ml	Dexmedetomidine 0.5 µg/ml
Sample size, n	40	39	45	41
Age, years	27.6 ± 3.7	28.3 ± 3.7	27.4 ± 3.4	28.8 ± 3.5
BMI, kg/m ²	24.1 ± 3.0	27.3 ± 2.4	27.0 ± 3.2	27.2 ± 2.4
Gestational age, weeks	39.3 ± 1.1	39.3 ± 1.0	39.1 ± 1.0	39.3 ± 2.0
Cervical dilation at epidural placement, cm	2.1 ± 0.3	2.2 ± 0.4	2.2 ± 0.4	2.1 ± 0.4
Epidural analgesia to cervix complete, min	240 (140, 344)	195 (115, 316)	240 (154, 421)	220 (143, 300)
Epidural analgesia to delivery, min	289 (226, 401)	255 (176, 377)	307 (193, 502)	278 (186, 403)
Caesarean delivery, n (%)	2 (5.0)	2 (5.1)	4 (8.9)	5 (12.2)
Pain relief satisfaction score, 1-5	4.2 ± 0.4*	4.4 ± 0.4	4.7 ± 0.6	4.4 ± 0.5
Neonatal weight, g	3332 ± 373	3366 ± 425	3285 ± 433	3339 ± 408
1-min Apgar score	8.8 ± 0.5	8.7 ± 0.7	8.8 ± 0.5	8.7 ± 0.6
5-min Apgar score	9.9 ± 0.4	9.9 ± 0.2	10.0 ± 0.0	9.9 ± 0.4
Umbilical artery pH	7.29 ± 0.04	7.30 ± 0.03	7.30 ± 0.03	7.30 ± 0.04

Data are shown as Mean ± SD, median (interquartile range) and number (%) as appropriate. *Adjusted P < 0.05, compared with dexmedetomidine groups.

Fang BY, Shen YL, Jin X, et al. Comparison of epidural dexmedetomidine to fentanyl in reducing regurgitation dose in Programmed Intermittent Epidural Release plus Patient-Controlled Epidural Analgesia during labor: a randomized, controlled, double-blind, parallel, multicenter study. *Frontiers in Anesthesiology*. 2022;16:1032. doi:10.3389/fan.2022.982828

19

PRACTICE

TABLE 2. Side effects and required patient-controlled epidural analgesia of epidural 2 µg/ml fentanyl versus three different concentrations of dexmedetomidine.

	Fentanyl 2 µg/ml	Dexmedetomidine 0.3 µg/ml	Dexmedetomidine 0.4 µg/ml	Dexmedetomidine 0.5 µg/ml	P value
Sample size	40	39	45	41	-
Pruritus	7 (17.5)*	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Bromage score > 1	2 (5.0)	1 (2.6)	3 (6.7)	9 (22.0)	0.007
Hypotension	3 (7.5)	3 (7.6)	5 (11.1)	7 (17.1)	0.635
Maternal Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Fetal bradycardia	2 (5.0)	5 (12.8)	3 (6.7)	2 (4.9)	0.483
Sleeping	3 (7.5)	1 (2.6)	0 (0.0)	2 (4.9)	0.294
Severe Sedation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Nausea and vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Patient required PCA	33 (82.5)*	17 (44.4)	20 (44.4)	9 (22.0)	0.005
Frequency of PCA	3 (1), 3*	0 (0, 2)	0 (0, 2)	0 (0, 2)	<0.001

Data are shown as number (%), median (interquartile range).
*Adjusted P < 0.05, compared with dexmedetomidine groups. Hypotension was defined as a decrease > 20% from baseline blood pressure, or as absolute value < 90 mm Hg. Bradycardia was defined as heart rate < 50 bpm. Jin-Ying Fang & Yi-Yao Shen. Y. FES.

Fang BY, Shen YL, Jin X, et al. Comparison of epidural dexmedetomidine to fentanyl in reducing regurgitation dose in Programmed Intermittent Epidural Release plus Patient-Controlled Epidural Analgesia during labor: a randomized, controlled, double-blind, parallel, multicenter study. *Frontiers in Anesthesiology*. 2022;16:1032. doi:10.3389/fan.2022.982828


20

PRACTICE

INTRATHECAL DOSING

SINGLE SHOT SAB / CSE

2.5-10 mcg



21

PRACTICE

Table 3: Comparison of mean and standard deviation of sensory block and motor block in four groups

Time (min)	Mean±SD				P
	D2.5	D5	D7.5	PBO	
Sensory block					
Onset of sensory block after SA (min)	5.36±0.718	4.33±0.758	2.83±0.746	7.27±0.739	<0.001
The time to achieve sensory block to T12/L1 and wearing off of sensory block	120.67±5.66	132.43±5.56	141.17±5.11	101.10±5.040	<0.001
Time to achieve motor block to ≥6 (using pin prick test every 1 min)	6.37±0.718	5.33±0.758	3.80±0.714	8.26±0.739	<0.001
Motor block					
Onset of motor block after SA	9.33±0.711	8.33±0.758	6.80±0.714	11.26±0.739	<0.001
Time to achieve motor block to ≥6 (Bromage Grade 3) (min)	11.33±0.711	10.33±0.758	8.80±0.714	13.26±0.739	<0.001
Time to achieve Bromage 0 or 1 and wearing off of motor block	134.30±5.873	148.60±6.066	163.13±5.99	119.10±6.098	<0.001

SD: Standard deviation; PBO: Placebo; SA: Spinal anesthesia.

Table 4: Comparison of mean and standard deviation of pain in the four studied groups

Pain	Group, mean±SD				P
	D2.5	D5	D7.5	PBO	
Recovery					
0.500±0.508	0.366±0.490	0.133±0.345	0.810±0.402	0.078	
1 h postoperative	0.500±0.508	0.366±0.490	0.133±0.345	1.633±0.490	<0.001
2 h postoperative	0.500±0.508	0.366±0.490	0.133±0.345	2.533±0.628	<0.001
4 h postoperative	1.500±0.508	1.166±0.379	1.033±0.182	3.333±0.606	<0.001
6 h postoperative	1.866±0.345	1.733±0.500	1.300±0.466	3.733±0.639	<0.001
12 h postoperative	2.733±0.449	2.033±0.319	1.866±0.434	4.933±0.764	<0.001

SD: Standard deviation; PBO: Placebo.

Madr N, Yazici B, Shalqou M, Hameem M, Madi A, Mohammedi B. Comparing the efficacy of different doses of intrathecal dexmedetomidine on hemodynamic parameters and block characteristics in labor. *Frontiers in Anesthesiology*. 2022;16:1032. doi:10.3389/fan.2022.982828

22

PRACTICE

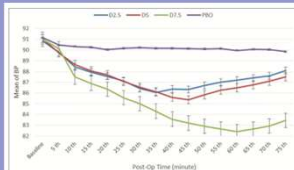


Figure 2: The trend comparison in mean of blood pressure in the four studied groups

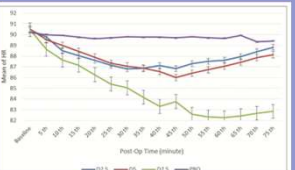


Figure 3: The trend comparison in mean of heart rate in the four studied groups

Madr N, Yazici B, Shalqou M, Hameem M, Madi A, Mohammedi B. Comparing the efficacy of different doses of intrathecal dexmedetomidine on hemodynamic parameters and block characteristics in labor. *Frontiers in Anesthesiology*. 2022;16:1032. doi:10.3389/fan.2022.982828

23

PRACTICE

TABLE 3 | Intraoperative adverse reactions [n(%)], vasoactive drugs [times], fentanyl (µg) and neonatal conditions.

Variable	PLACESO				P-value
	5 mcg Group R (n = 30)	5 mcg Group RD1 (n = 30)	7.5 mcg Group RD2 (n = 30)	10 mcg Group RD3 (n = 30)	
Chills [n(%)]	14(46.7)	4(13.3)*	4(13.3)*	3(10.0)*	<0.001
Nausea [n(%)]	12(40.0)	9(30.0)	8(26.7)	9(30.0)	0.053
Vomiting [n(%)]	4(13.3)	5(16.7)	6(20.0)	5(16.7)	0.233
Hypotension [n(%)]	18(60.0)	17(56.7)	20(66.7)	18(60.0)	0.938
Bradycardia [n(%)]	5(16.7)	4(13.3)	9(30.0)	5(16.7)	0.373
Vasoactive traction Response [n(%)]	7(23.3)	6(20.0)	6(20.0)	5(16.7)	0.885
Fentanyl consumption (µg)	0.50	0.35	0.35	0.3	0.797
Asoprine (times)	2	2	3	3	0.835
Phenylephrine (times)	28	37	69*	73*	0.007
Newborn weight(kg)	3365 ± 372	3334 ± 336	3275 ± 375	3307 ± 327	0.788
Apgar 1 min	10 (10,10)	10 (10,10)	10 (9,10)	10 (9,10)	0.295
Apgar 5 min	10 (10,10)	10 (10,10)	10 (10,10)	10 (10,10)	1

Data are presented as a number or means ± SD or median and range or numbers and percentages. Fentanyl consumption = total dose of fentanyl consumption during the operation. *p < 0.05 compared with Group R.

Madr N, Yazici B, Shalqou M, Hameem M, Madi A, Mohammedi B. Comparing the efficacy of different doses of intrathecal dexmedetomidine on hemodynamic parameters and block characteristics in labor. *Frontiers in Anesthesiology*. 2022;16:1032. doi:10.3389/fan.2022.982828

24

REFERENCES

- Kumar S, Choudhury B, Varikasavu SR, et al. A systematic review and meta-analysis of efficacy and safety of dexmedetomidine combined with intrathecal bupivacaine compared to placebo. *Cureus*. Published online December 12, 2022. doi:10.7759/cureus.32425
- Li N, Hu L, Li C, Pan X, Tang Y. Effect of epidural dexmedetomidine as an adjuvant to local anesthetics for labor analgesia: A Meta-Analysis of Randomized Controlled Trials. *Evidence-based Complementary and Alternative Medicine*. 2021;2021:1-11. doi:10.1155/2021/4886970
- Liu X, Qian J, Bei S, Xiao F, Shen H. Intrathecal dexmedetomidine can decrease the 95% effective dose of bupivacaine in spinal anesthesia for cesarean section. *Medicine*. 2023;98(9):e14666. doi:10.1097/med.00000000000014666
- Modir H, Yazdi B, Shokrpour M, Hesamini R, Modir A, Mohammadbeigi A. Comparing the efficacy of different doses of intrathecal dexmedetomidine on hemodynamic parameters and block characteristics with ropivacaine spinal anesthesia for cesarean section: A double-blind, randomized clinical trial. *The Indian Anaesthetist Forum*. 2020;23(1):1-6. doi:10.4103/theiaforum.theiaforum_41_19
- Pang RX, Shen YH, Jin X, et al. Comparison of epidural dexmedetomidine to fentanyl in reducing ropivacaine dose in Programmed Intermittent Epidural Bolus plus Patient Controlled Epidural Analgesia during labor: A randomized, double-blind, controlled study. *Frontiers in Medicine*. 2022;9. doi:10.3389/fmed.2022.935643
- Singh S, Bansal P, Dureja J. Off-label use of drugs in regional anesthesia: A need for setting up policies. *Journal of Anaesthesiology Clinical Pharmacology*. 2017;33(4):448. doi:10.4103/joacp.joacp_341_15
- Sun Y, Xu Y, Wang G n. Comparative evaluation of intrathecal bupivacaine alone, bupivacaine-fentanyl, and bupivacaine-dexmedetomidine in caesarean section. *Drug Research*. 2014;65(9):468-472. doi:10.1053/s-0034-1387740
- Shen QH, Li H, Zhou X, Yuan XZ, Lu Y. Dexmedetomidine as an adjuvant for single spinal anesthesia in patients undergoing cesarean section: a system review and meta-analysis. *Journal of International Medical Research*. 2020;48(5):03000052091342. doi:10.1177/030000520913423
- Zhang Q, Xia LV, Li W, et al. Intrathecal dexmedetomidine combined with ropivacaine in cesarean section: A prospective Randomized Double-Blind Controlled study. *Frontiers in Medicine*. 2022;9. doi:10.3389/fmed.2022.922611
- Zhou H, Wen J, Guo G, Zhao Y, Liu W. Evaluation of the effect of dexmedetomidine combined with ropivacaine in epidural labor analgesia: a systematic review and meta-analysis. *Minerva Anestesiol*. 2022;28(10):844-852. doi:10.23736/2075-9393.22.10.264-x