Transient Coma Due To Epidural Anesthesia: The Role of Loss of Sensory Input

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Christopher Dardis**
DEF 2 **David Lawlor**
EF 1 **Courtney M. Schusse**

1 Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, U.S.A.
2 Department of Anesthesia, Blackrock Clinic, Dublin, Ireland

Corresponding Author: Christopher Dardis, e-mail: christoherdardis@gmail.com
Conflict of interest: None declared

Patient: **Female, 22**
Final Diagnosis: **Coma due to loss of sensory input**
Symptoms: **Coma**
Medication: **Lidocaine**
Clinical Procedure: **Epidural**
Specialty: **Anesthesiology**

Objective: **Unknown ethiology**
Background: Epidural anesthesia is the most commonly used method of pain relief during labor in the USA. It is not classically associated with alterations in level of alertness. Coma during the procedure is rare, with a reported incidence of 0.1–0.3%.
Case Report: An otherwise healthy patient experienced almost complete loss of brainstem function following routine epidural anesthesia during delivery. The episode lasted for less than 3 hours and the patient made a full recovery. To our knowledge, this is the most detailed clinical observation to date of this condition.
Conclusions: Clinicians should be aware of this rare and potentially serious complication of epidural anesthesia. The case highlights the need for sensory input to maintain alertness through the activity of the ascending reticular activating system.

MeSH Keywords: **Anesthesia, Epidural • Anesthesia, Spinal • Coma • Evoked Potentials, Auditory, Brain Stem**

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/895384

📄 2278   ⊞ 1   📊 2   📖 18

Background

It is estimated that more than 50% of women delivering in hospital use epidural anesthesia in the USA [1]. Despite approximately 4 million births per year in the USA, serious neurological complications resulting from this technique are exceptionally rare. One review of 27 000 cases showed an incidence of just 0.01% where there was "a relatively protracted period of real concern" [for the mother's safety] [2].

Given the frequency of epidural use, even rare complications are likely to be encountered by the practicing physician. While lethargy following this form of anesthesia is well recognized in practice, the sudden and unexpected onset of coma is always a matter of concern. As shown below, we believe this impaired alertness to be due to the loss of spinal cord sensory input to the brainstem. Reassuringly, such episodes reverse rapidly without needing special management beyond supportive care. This phenomenon should also be of interest of those studying the mechanisms by which alertness is sustained.

The condition known as "massive epidural" or "total spinal analgesia following epidural analgesia" entered the medical literature in 1956 with a report of 3 cases. There was doubt as to the correct positioning of the epidural needle in each [3]. The cases were characterized by the following features:
• Complete loss of consciousness;
• General flaccidity (including the vocal cords);
• Fixed and dilated pupils;
• Stable blood pressure;
• Respiratory failure requiring artificial ventilation;
• Complete recovery within 45–120 min;
• No sequelae.

Such episodes received attention in the first 'systematic review' of the complications of epidural anesthesia, in 1969, where an incidence of 0.1–0.3% was estimated [4]. The author comments that [our italics]:

"Many theories have been advanced for this peculiar occurrence but none will fit all the facts. Fortunately no fatal case has been reported and therefore post-mortem findings are not available. While it is true that some transudation across the dura mater from the extradural space does occur, experiments have shown that the *maximum effect does not take place until 40 minutes have elapsed*, so that it is doubtful if this is a factor. Suffice it to say that there are many aspects of extradural block which do not admit of rational explanation and this is one of them."

Since then, the condition has received little attention, perhaps on account of its transient and fully reversible nature. A typical case follows, along with a review of some more recent literature which helps to explain the pathophysiology at work.

Case Report

The patient was a 22-year-old primiparous white woman, who presented at 40 weeks gestation with rupture of the membranes. She had previously been in good health and the pregnancy had been unremarkable, including thyroid function tests. She had no history of substance abuse. Blood tests and urinalysis on admission were normal apart from expected dilutional anemia.

Intravenous (IV) oxytocin was started as standard procedure shortly after admission. Labor commenced 5½ h later. Analgesia was achieved by IV morphine sulphate via patient-controlled analgesia (PCA) and epidural lidocaine 1.5%.

During her 4 h labor, the patient received a total dose of 6 mg of morphine via PCA. Over the same time period, she received a total of 60 ml of a solution of lidocaine 1.5% (total dose of lidocaine 600 mg) with epinephrine 1:200 000. The placement was confirmed by lack of cerebrospinal fluid (CSF) leak from the catheter. No 'test' dose of lidocaine was administered.

At this time a decision to proceed to cesarean section was made because labor was not progressing. She was given an additional bolus of epidural lidocaine (5 ml=50 mg) prior to surgery. She became unresponsive shortly thereafter and no further analgesia was given. Her airway remained patent with regular breathing. The patient's blood pressure (BP) and heart rate remained stable throughout the procedure, at 110–125/65–80 mmHg and 65–80 /min, respectively. These readings were similar to those at admission and to those taken during clinic visits throughout her pregnancy. Supplemental oxygen was administered throughout surgery, which was completed within 20 min. The infant's APGAR scores were 10/10 on repeated measurements.

A detailed neurological exam 1½ h later (6 h after starting the epidural) was performed while she remained in the recovery room. This showed the following:
• Eyes closed; pupils fixed and unreactive, measuring 5 mm;
• No response to pain (nail bed pressure);
• Absent corneal and oculocephalic reflexes;
• No movement of the eyes with cold caloric stimulation;
• Decreased muscle tone throughout (almost flaccid);
• Diminished reflexes: biceps 1+; Babinski's reflex was absent; no other reflexes could be elicited;
• Regular, deep breathing at a rate of 12/min without support; no cyanosis was present.

Within 30 min she began to recover. This was manifest initially by the return (almost simultaneously) of all brainstem reflexes along with sensitivity to pain; muscle power recovered to at least 4+/5 throughout (as assessed by withdrawal from pain).

Within another 30 min she could open her eyes when spoken to and was able to say her name and also "I feel very tired"; she could easily follow instructions, such as "squeeze my hand". She remained drowsy, limiting a more detailed assessment of mentation. Her muscle tone remained decreased and reflexes at the knees and ankles remained absent (although it was not possible to perform re-enforcement). Power was at least 4+/5 throughout. She was moved to a ward for additional observation.

Within another 4 h she had recovered fully. Blood tests, performed at coma onset and the following day, were unremarkable: complete blood count, comprehensive metabolic panel, magnesium, TSH, and blood cultures. An MRI of the brain was performed, which was entirely normal. She was discharged on post-operative day 2 without incident.

Discussion

This case is typical of the phenomenon known as "massive epidural". The neurologic exam and the stages of recovery are described in more detail here than in previous reports. The MRI of the brain is also reassuring; we acknowledge that the test may have been unnecessary.

Mechanism

We propose that the mechanism at work here is 'sensory de-afferentation dependent sedation', leading to the impairment of brainstem transmission. In particular, the ascending reticular activating system (ARAS) appears to require sensory input in order to continue to maintain alertness. This is a logical extension of the experimental work below, particularly that performed with volunteers undergoing epidural anesthesia while measurements were taken of brainstem function, as well as of sedation [5].

The use of morphine can be seen as a predisposing factor, although it is neither necessary nor sufficient to explain the depth of coma reached. If this were the case, we would have expected the patient to have 'pinpoint' pupils. The half-life of morphine IV in young adults is around 2 h; therefore, the initial dose of 2 mg given over the first hour would be expected to have almost completely worn off by the time coma developed.

Clinical observations

Epidural (as well as spinal) anesthesia has long been recognized to reduce the drug dosages necessary to achieve CNS sedation or coma (e.g., with thiopental, midazolam, isoflurane, sevoflurane, and propofol) [6]. Furthermore, the higher potency bupivacaine (*vs.* lidocaine) has been reported to reduce the dose of anesthetic necessary to maintain general anesthesia for surgery [7].

A summary of clinically observed cases, including our own, as well as the experimental protocols that follow, is shown in Table 1. To enable comparison between different anesthetic agents, the doses have been converted to moles (mol). We recognize that this does not account for relative potency or differences in patient habitus. Furthermore, in the pregnant patient, the volume of subarachnoid space is likely to be smaller owing to pressure from the gravid uterus [5].

Experimental work

The question has been raised as to whether the systemic absorption of epidural anesthesia may be responsible for some of its observed effects. Evidence against this comes from a randomized trial of lidocaine given via epidural or IV to patients recovering from surgery under standard inhalational anesthesia. Despite the higher systemic levels of lidocaine in the IV group, they recovered more slowly from coma [8].

A technique closely related to epidural anesthesia is spinal anesthesia. One authority has noted that "the only real differences [between the techniques] are the site of injection and the volume of anesthetic used" [9]. The differences are illustrated in Figure 1. While there is more systemic absorption of local anesthetic from the epidural space (due to its rich venous plexus), this is likely to have little bearing on loss of sensory input.

Both epidural and spinal anesthesia have been studied in volunteers to clarify the mechanism responsive for the sedation seen with these techniques [5,10]. To quantify alertness, these studies used techniques that have been recommended in the operating room. The use of these measures remains far from routine:

1. The bispectral index (BIS) is a measure derived from EEG. It is recommended in the British National Institute for Health and Care Excellence (NICE) Guidelines as an option during any type of surgery in patients at higher risk of awareness during surgery or of excessively deep anesthesia and in all patients receiving total intravenous anesthesia [11]. A meta-analysis concluded that it aids "postoperative recovery from relatively deep anesthesia" [12].

2. Brainstem auditory evoked potentials (BAEPs) (Figure 2). In a randomized trial in cardiac surgery, these have been shown

Table 1. Details of various anesthetics used in the literature cited.

Paper	ID	Age	GA	Dose	LA	Pot.	Route	Length (min)	Dose (mg)	Dose (mmol)	Dur. (min)
Clinical											
De Saram [4]	1	55	None	NA	L	M	E	NA	175	0.61	125
	2	39	H	900 mg	L	M	E	NA	400	1.4	240
	3	50	H	900 mg	L	M	E	NA	400	1.4	240
Boys* [6]		35	None	NA	B	H	E (?S)	195	10→30	0.03→0.09	NA
Current		22	None	NA	L	M	E	240	600→50	2.1→0.2	150
Experimental											
Doufas [7]		18–45	None	NA	C	M	E	Max 300	Max 1000	3.7	NA
Inagaki [9]		26–45	I	NA	L	M	E	149±22.5	→210	0.9	20
Pollock [12]		38 +- 10	None	NA	L	M	S	Mean 90	→50	→0.18	NA

NA – not applicable/ not available; Age – for case series, this is given as range (min – max) or mean ± standard error (m ± se);
GA – general (systemic) anesthetic: H – hexobarbitone; I – isoflurane; LA – local anesthetic: L – lidocaine; B – bupivacaine;
C – chloroprocaine; Pot. – potency: M – medium; H – high; Route: E – epidural; S – spinal. Length of anesthesia (for clinical cases, this refers to time from initial injection to coma): mean ± standard error. Dose: → represents bolus given just before onset of coma;
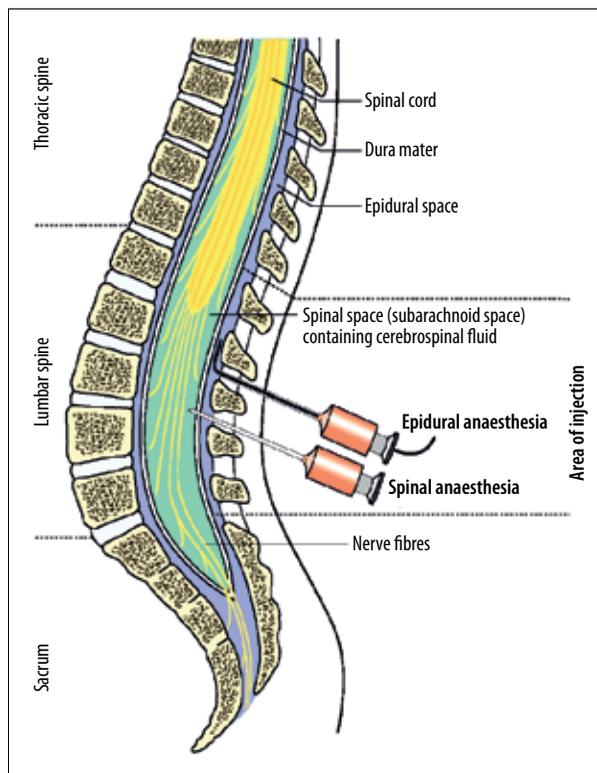Dur. – duration of coma (time to return of alertness).

Figure 1. Differences between epidural and spinal anesthesia. In spinal anesthesia, the anesthetic is administered into the CSF, whereas in epidural anesthesia it is infusion into the potential space external to the dura mater.

to reduce the dose requirement for anesthetic agents and the need for intraoperative vasopressors [13]. Changes in the BAEP index has also been suggested to be more useful than BIS in monitoring the induction of anesthesia, particularly for ketamine [14].

The BIS correlated poorly with self-rated sedation. This is likely to reflect the 'reference library' against which the EEG is compared to find an optimal match. This (proprietary) library is thought to comprise subjects undergoing inhalational anesthesia. Interestingly, in the study of spinal anesthesia, sedation peaked 60 min *after* the anesthetic injection, long after local levels of anesthetic were declining.

In the epidural study, the only correlate of depth of sedation was BAEP wave III. This measures the electrical activity of the inferior colliculus, which receives input from the spinothalamic tracts and the medial lemniscus; when active, it increases cortical activity through its influence on ascending cholinergic and serotonergic pathways. It is thought to be a key anatomic mediator of the increased alertness that occurs with the startle reflex.

Referring again to Table 1, it is certainly striking that a number of these cases occurred soon after the injection of a small additional bolus of anesthetic. Comparison of doses is complicated by differing dosing regimens and durations of anesthesia. However, the common theme is that this bolus pushed
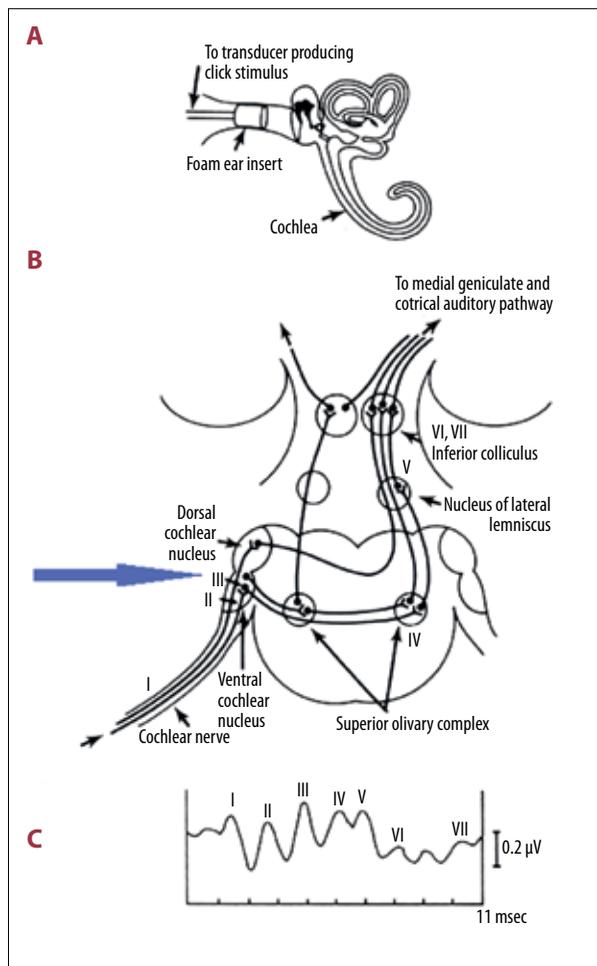
Figure 2. Overview of BAEPs. (**A**) Technique. (**B**) Structures involved; the origin of wave III is highlighted. (**C**) Waves (typical recording).

already-sedated patients 'over the edge' into coma, by further decreasing spinal cord input, resulting in a corresponding loss of brainstem function.

Our case is, clinically, the most closely observed to date; like coma from any cause, respiration is the last reflex to disappear. Complete loss and recovery of the other brainstem reflexes appears to occur almost simultaneously.

Implications and future directions

Some relatively newer techniques should provide additional information as to the mechanisms at work in this form of sedation:
1. Functional MRI (fMRI) has much finer spatial resolution than EEG and allows for assessment of functional networks, particularly cortical.
2. Magnetoencephalography (MEG) has the advantage (*vs.* EEG) of more accurate measurement of structures below

the brain surface, thus lending itself to quantifying brainstem activity. BAEPs have been studied in this way [15].

Both lend themselves to the experimental setting. While safety is always paramount, there is clearly a level of 'deep' anesthesia achievable with the technique where ventilation is not impaired.

MEG is limited by availability; at the time of writing there are less than 25 such devices operational in the USA. fMRI has the advantage that it may be used intra-operatively; a standard 1.5 T MRI can be adapted for this purpose [16]. It has been studied in patients undergoing anesthesia with the inhaled agent sevoflurane; as expected, there is widespread loss of cortical connectivity, particularly the motor cortex [17].

In coma induced by epidural/spinal anesthesia (*vs.* inhalational or GABA-potentiating techniques), the effect on cortical synaptic transmission appears to be minimal. Thus, the contribution of the ARAS to cortical connectivity could readily be studied by one or both of the above techniques.

Conclusions

Our patient lost consciousness due to impaired sensory input, which is required for alertness. Why this occurs only rarely remains unclear. Spread to the subdural space has been suggested as a possible cause [18]. The latter appears attractive theoretically – the slow rate of spread is consistent with the gradual clinical onset of symptoms, and the dorsal distribution may account for the relatively small effect on BP. An alternative explanation, that some individuals are much more sensitive to this form of anesthesia, cannot be excluded; however, there are no reports of recurrent episodes in the same patient. Also, these individuals appear to be at no greater risk of other adverse reactions to medications.

Regarding nomenclature: the terms "massive epidural" and "total spinal analgesia following epidural analgesia", while of undoubted historical importance, do not emphasize the pathogenesis of this condition and may be puzzling for the non-specialist. We propose the term "(transient) coma due to loss of sensory input" as more descriptive and easier to understand for the general physician.

This 'coma due to loss of spinal sensory input' may be encountered by any clinician caring for a patient undergoing epidural anesthesia. Once the phenomenon is recognized, we suggest that no further investigations are required; the patient and family may be reassured once the coma resolves. The study of this form of coma offers the chance to clarify some of the basic mechanisms responsible for maintaining alertness.

References:

1. Vincent RD Jr, Chestnut DH: Epidural analgesia during labor. Am Fam Physician, 1998; 58(8): 1785–92

2. Crawford JS: Some maternal complications of epidural analgesia for labour. Anaesthesia, 1985; 40(12): 1219–25

3. De Saram M: Accidental total spinal analgesia; a report of three cases. Anaesthesia, 1956; 11(1): 77–79

4. Dawkins CJ: An analysis of the complications of extradural and caudal block. Anaesthesia, 1969; 24(4): 554–63

5. Conklin KA: Pharmacology of local anesthetics. AANA J. 1987; 55(1): 36–44

6. Doufas AG, Wadhwa A, Shah YM et al: Block-dependent sedation during epidural anaesthesia is associated with delayed brainstem conduction. Br J Anaesth, 2004; 93(2): 228–34

7. Yadav G, Pradhan CS, Gupta SK et al: Comparison of sedative efficacy of epidural bupivacaine 0.5% with lignocaine 2% plus adrenaline by measuring BIS guided propofol requirement in gynaecological surgery. Anaesth Pain Intensive Care, 2012; 16(1)

8. Inagaki Y, Mashimo T, Kuzukawa A et al: Epidural lidocaine delays arousal from isoflurane anesthesia. Anesth Analg, 1994; 79(2): 368–72

9. Vandam L: Neurological sequelae of spinal and epidural anesthesia. Int Anesthesiol Clin, 1986; 24(4): 231–55

10. Pollock JE, Neal JM, Liu SS et al: Sedation during spinal anesthesia. Anesthesiology, 2000; 93(3): 728–34

11. National Institute for Clinical Excellence. NICE Diagnostics Guidance: Depth of anaesthesia monitors – Bispectral index (BIS), E-Entropy and Narcotrend Compact M, 2012

12. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N: Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev, 2014; 6: CD003843

13. Jildenstål PK, Hallén JL, Rawal N et al: Effect of auditory evoked potential-guided anaesthesia on consumption of anaesthetics and early postoperative cognitive dysfunction: a randomised controlled trial. Eur J Anaesthesiol, 2011; 28(3): 213–19

14. Matsushita S, Oda S, Otaki K et al: Change in auditory evoked potential index and bispectral index during induction of anesthesia with anesthetic drugs. J Clin Monit Comput, 2015; 29(5): 621–26

15. Parkkonen L, Fujiki N, Mäkelä JP: Sources of auditory brainstem responses revisited: contribution by magnetoencephalography. Hum Brain Mapp, 2009; 30(6): 1772–82

16. Gasser T, Ganslandt O, Sandalcioglu E et al: Intraoperative functional MRI: implementation and preliminary experience. Neuroimage, 2005; 26(3): 685–93

17. Peltier SJ, Kerssens C, Hamann SB et al: Functional connectivity changes with concentration of sevoflurane anesthesia. Neuroreport, 2005; 16(3): 285–88

18. Boys JE, Norman PF: Accidental subdural analgesia: A case report, possible clinical implications and relevance to "massive extradurals". Br J Anaesth, 1975; 47(10): 1111–13