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# Cauda equina syndrome and arachnoiditis from an epidural dose of chloroprocaine injected subdural: Farewell to a local anesthetic

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## SUMMARY

Chloroprocaine (CHLP) has undergone controversies related to its low pH, preservatives and antioxidants. In a recently delivered parturient scheduled to have a postpartum tubal ligation using the same catheter as for labor, aspiration was negative, The test dose with the anesthetic failed to indicate intrathecal or intravascular injection; delayed onset, led to further doses; after 15 mL had been given, arterial hypotension and sensory block was noted at T5, 10 mL more were given reaching a C5 level after a total dose of 25 mL had been completed. The slow onset suggested subdural injection; subsequently, the patient developed cauda equina and arachnoiditis suggesting that the dose intended for epidural anesthesia eventually entered the intrathecal space.

**Key words:** Chloroprocaine, subdural, cauda equina, arachnoiditis, epidural anesthesia, tubal ligation.

## *RESUMEN*

*La cloroprocaína (ClPr) ha atravesado por controversias en relación con su bajo pH, con los conservantes y con los antioxidantes. En una paciente parturienta que había dado a luz recientemente, y que se encontraba programada para tener una ligadura de trompas postparto, usando el mismo catéter utilizado en el trabajo de parto, la aspiración fue negativa. La dosis de prueba con el anestésico falló para indicar la inyección intratecal o intravascular; y el hecho de que ocurriera una demora, condujo a dosis adicionales. Luego de que se hubieron suministrado 15 mL, se observó hipotensión y bloqueo sensorial a T5. Se suministraron 10 mL más alcanzando un nivel C5 luego de que se hubiera completado una dosis de 25 mL. El lento establecimiento aconsejó el empleo de una inyección peridural (epidural); subsiguientemente, la paciente desarrolló cauda equina y aracnoiditis, lo que sugiere que la dosis planeada para la anestesia peridural eventualmente ingresó al espacio intratecal.*

***Palabras clave:*** *Cloroprocaína, subdural, cauda equina, aracnoiditis, anestesia peridural (epidural), ligadura de trompas.*

## INTRODUCTION

The reports of nine plus cases[1-4] of neurological deficits after the administration of chloroprocaine (CHLP), intended epidural, was followed by investigations that led to discover that it contained, as preservative, the antioxidant Na bisulfate. It was then decided to recommended for Extradural administration. The manufacturer then, made one preparation without the preservative and placed the label «for epidural and caudal, but not for spinal anesthesia» and placed the preparation contained in a ambar dark color vial[5]. These measures gave the impression that it was safe to use this medication extradurally, even when the feasibility of intradural injection or catheter migration could allow entry of this acid anesthetic into the subarachnoid space, where it has the potential to produce permanent neurological deficits. Herein a case of cauda equina syndrome and arachnoiditis with permanent serious neurological function occurred in a post partum patient given a substantial dose of 3% CHLP, after possible catheter migration; this matter is brought for discussion and for re-assessment, as CHLP, since 2005 to 2009, in small dosages, was evaluated as a possible spinal anesthetic in the ambulatory setting.

## CASE REPORT

A 27 year old black woman was admitted for delivery of a term pregnancy. She had one previous pregnancy delivered under epidural anesthesia with bupivacaine (BPV) infusion. Her A.S.A. physical status classification was II, due to obesity. The vital signs were BP 120/75, HR 78, respirations18 and Temp.was $97.0^0$F. Because she was in labor, an epidural catheter was inserted, giving test doses of lidocaine (LID) 2%, 2 mL, followed by 3 mL of 0.25% BPV, without showing any signs of intradural or intravascular injection. When cervical dilatation was 5 cm, an infusion of BPV and fentanyl was initiated. Labor progressed uneventfully and six and one half hour later, a baby boy with Apgar scores 6 and 9 at birth and at 5 minutes, was delivered. The patient was sent to the post-delivery ward.

Fourteen hours later, in the holding area, while the patient was prepared for a postpartum tubal ligation (PPTL) using catheter still taped on her back; control measurement of BP was 110/70; and the HR 83 bpm; although the catheter have been in place for 16 hrs it was decided to use it. As test of functioning, it was aspirated, revealing no fluid, therefore 2 mL of 3% CHLP were injected, followed two minutes later, by 3 mL of 3% CHLP without undue effects. Thereafter, two more dosages of 5 mL each, were given two minutes apart for a total of 15 mL of CHLP. The ABP dropped to 75/45, she received 10 mg of ephedrine IV; by then, 1,000 mL of Ringer's lactate solution had been given IV, then 30 mg more of ephedrine IV, raised the BP to 100/50. By then, the sensory level was T5.

Ten minutes later, 10 mL more of 3% CHLP were administered. The patient was moved to the OR where monitors were applied, the vital signs were BP 130/70, HR 118, Temp 97, Resp 22 and $SaO_2$ 100% on face mask. Surgery began 65 minutes from the start of anesthesia with the sensory level determined to extend from C5 to S4; respirations were described as «paradoxical» so she was given CPAP with a face mask; sedation was attained with titrated morphine and midazolam 2 mg IV, of each. In the PACU she was noted to have prolonged duration of the sensory (4.5 hours) and motor (3 hrs) blocks. The next day, she was unable to urinate on her own and did not had a bowel movement for 4 days; she continued to have weakness on both lower extremities and moderate to severe low back pain. A Neurology Consultant diagnosed her as having «lumbosacral neurodeficit; possible arachnoidittis». For the last three years, the patient has complained of moderate to severe lower back pain radiated to the sacral region, bilaterally; in addition, she has had dispareunia and sexual dysfunction with perineal numbness including the genitalia; she self-catheterizes her bladder three to four times a day and has had rectal incontinence intermittently. In two separate MRI examinations of the lumbar spine, taken 3 and 24 months after the date of the anesthetic, they both have shown «Clumping and adherence of the nerve roots to the dural sac at the lower lumbar and sacral segments» and «empty dural sac» (Figures 1 and 2) plus «degenerative changes in the L4-L5 complex».

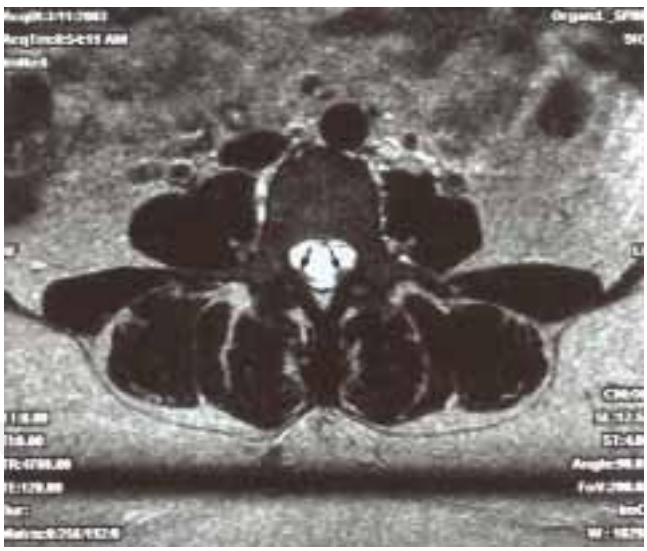

**Figure 1.** Axial view of an MRI of the lumbar spine showing two clumps of nerve roots at the left and right posterior corners of the dural sac (arrows), at the L4 level.

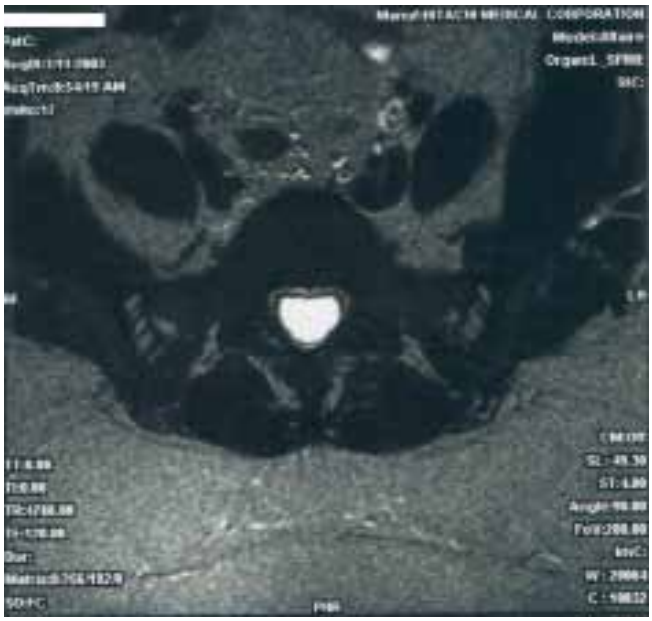

**Figure 2.** Axial view of an MRI depicting an image of an «empty sac» as the nerve roots are adhered to the wall of the dural sac.

## DISCUSSION

When Foldes et al[6] in 1952 introduced CHLP, they included 212 patients that received spinal anesthesia; when it was found that it contained preservatives, it became popular for epidural anesthesia[7]. In 1980, several cases of neurological deficits were reported after high sensory blocks from what appeared to be injections through misplaced epidural catheters[1-4]. A meeting of experts[8] reviewed the cases and described some of their own experiences. Laboratory studies suggested that Na bisulfite, used to stabilize a solution with pH between 2.8 and 3.4, could be the culprit[9-13]; Gissen et al[14,15] confirmed these observations. Thereafter, CHLP remained available, with the indication «for epidural and caudal anesthesia» and the warning, «but not for subarachnoid administration». Reports of lower back pain were found to be caused by EDTA[16], which was removed, but the labels remained unchanged.

Suspecting that CHLP was the cause of neural injuries Barsa et al[17] in a comparative, *in vivo* study, demonstrated neurotoxicity from CHLP alone and in combination with BPV, but not by LID or BPV alone. Kalichman et al[18] found that only CHLP could be implicated as producing long term nerve edema, but not its preservative, LID or BPV. Myers et al[19] noted that topical 3% CHLP and 1% tetracaine produced endoneurial edema while LID 2%, BPV 0.75% and 0.9% NaCl did not, concluding that the two ester-type local anesthetics having the lowest pH produced changes associated with neurotoxicity in the endoneurial environment, eventually creating fibrotic changes as late consequence of injury. Seravalli et al[20] in murine glial and hepatic cells, as well as in human fibroblasts reported that cell membrane fusion was not caused by procaine, lidocaine, Na bisulfite, nor by chloro-aminobenzoic acid and diethylamino ethanol (both chloroprocaine metabolites), but only by CHLP alone.

Lately, Taniguchi, Bolen and Drasner[21] noted that intrathecal injection in rats of either CHLP alone and CHLP plus Na bisulfite produced the greatest sensory impediment and morphological nerve injury findings, while neither saline nor Na bisulfite alone produced signs of neurotoxicity. Although questioned by Lambert[22], this study, thus far, has not been challenged.

Currently, the generic form of CHLP contains Na bisulfite with the indication «For peripheral nerve block and infiltration»; the non-generic indicates «for caudal and epidural anesthesia only» plus the clear warning «not for intrathecal anesthesia». This cautious advice ignored that not uncommonly, incidental dural punctures occur and epidural catheters may migrate to the subdural or to the subarachnoid spaces. By removing the bisulfite from CHLP, a false sense of security has resulted assuming that all presentations of this anesthetic could be used inside of the vertebral canal, as long as it was kept extradural. Winnie and Nader[5] cautioned about having two presentations (with and without preservative) in similar glass containers, dark vials have been provided by at least one manufacturer.

Moore[23] warned about the dangers of a confusing label indicating «epidural yes, subarachnoid no», because incidental dural punctures do occur even in the hands of the most experienced. Horlocker[24] has also questioned the dual meaning of such indication that may under unusual circumstances expose the nerve roots and the spinal cord to a high dose of an acid local anesthetic, that if given intrathecal, may trigger a chain of inflammatory events leading to neurological deficits and arachnoiditis[25-27].

Due to its rapid onset and short duration, CHLP is favored by some[28] while others avoid it[29]. A treatise reviewing «Evidence based Medicine in Obstetric Anesthesia» did not include this anesthetic in the index[30]. In the case described, an epidural catheter used for labor analgesia for over 16 hours, then left 14 more hours postpartum may have migrated to the subdural space, as confirmed by negative aspiration of the catheter and the slow onset of sensory anesthesia. Local anesthetics deposited in this compartment have been noted to pass at a slower rate toward the CSF[27], so they are considered unpredictable; Chestnut[26] suggested that if PPTL's are delayed more than 8 hours, it is preferable to administer a spinal anesthetic. In 19 cases, in whom the consequences from epidural catheters «going astray» by migration reviewed by Reynolds[27] unintended subdural injections of «epidural doses» of local anesthetics produced «high blocks»; however, only those that received CHLP developed permanent neurological sequelae, while none of those receiving either LID or BPV had permanent neurological impairment.

Lately, Kopacz and collaborators[31-39] began clinical trials using chloroprocaine for spinal anesthesia. They compared it to procaine, lidocaine and bupivacaine, conducted dose-effect observations and noted the effect of adding (clonidine, epinephrine, dextrose or fentanyl). Casati et al[40, 41] conducted controlled, double blind studies in small groups of patients finding no adverse effects; recognizing prompt onset and short recovery as advantages. The methodology of these studies, was questioned by Drasner[42] who pointed out that laboratory studies had not preceded clinical trials, noticing that some volunteers received two spinal anesthetics either seven days or even two days apart, besides, the groups of patients given CHLP were too small; the only favorable result was a shorter average time to discharge. Palas[43] reported short lasting spinal anesthetics with 1% CHLP, but this authors did not report side effects. A recent review[44] of over 600 patients having ambulatory surgery under spinal anesthesia with low dosages of CHLP, reported shorter recovery stay, but had a significantly larger incidence of side effects (47 *vs* 10) than intrathecal LID or BPV, that is more than the two amides, together. Is the time gained, worth the risk?

The apparent lack of neurotoxicity of preservative free CHLP, when given in small dosages (40 to 70 mg) intrathecal, needs to be investigated further. Since neural injuries observed in various laboratory preparations[9-15,17-21], earlier clinical cases[1-4,26] plus the report herein described, refer mostly to the consequences from large dosages (600 to 1,000 mg) of CHLP, incidentally administered subdural or subarachnoid; should the FDA consider reversing the warning to «for spinal but not for epidural» anesthesia? I hope not.

Without much fanfare and in lieu of two surprising discoveries of research fraud[45,46], this dilemmas seem to have been solved by the Editorial Boards of most serious Anesthesia-related journals who have implemented stringent norms in order to only accept manuscripts dealing with new medications, or local anesthetics which have been suspected to have neurotoxicity if they comply with specific requirements. One of them is that the potential authors will have to submit their research protocol, to the Editorial Board of the Journal, to which they intend to submit their final manuscript, for presumptive approval, before the studies get under way. This and other measures should prevent questionable interpretations, dangerous exposure of patients to hazardous doses of medications or worse to injure paid volunteers. We must ask ourselves, knowing what we know, should we continue to inject an acid medication (pH 2.8 to 3.2) into the delicate subarachnoid space, so patients may be discharged 12 minutes earlier? Our main duty is to protect patients from any hazards, then we may be concerned about Operating Rooms utilization or send patients home 7 minutes earlier.

## REFERENCES


1. Conklin KA, Van der Wall C. Epidural anaesthesia with chloroprocaine. Delayed onset, extensive spread, prolonged duration. Anaesthesia 1980;35:202-4.
2. Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 1980;59:452-4.
3. Ravindran RS, Bond VK, Tasch MD, et al. Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 1980;59:447-51.
4. Moore DC, Spierdijk J, van Kleef MD, Coleman DL, et al. Chloroprocaine neurotoxicity: four additional cases. Anesth Analg 1982;61:2:155-159.
5. Winnie AP, Nader AM. Santayana's prophecy fulfilled. Reg Anesth Pain Med 2001:26:558-64.
6. Foldes FF, McNall PG. 2-chloroprocaine: a new local anesthetic agent. Anesthesiology 1952;13:287-96.
7. Foldes FF, Colavinzenso JW, Birch JH. Epidural anesthesia: A reappraisal. Anesth Analg 1956;34:89-100.
8. Covino BG, Marx GT, Finster M, Zsigmond EK. Prolonged sensory/motor deficits following inadvertent spinal anesthesia. Anesth Analg 1980;59:399-400.
9. Ravindran RS, Turner MS, Muller J. Neurologic effects of subarachnoid administration of 2-chloroprocaine-CE, bupivacaine, and low pH normal saline in dogs. Anesth Analg 1982;61:3:279-28.
10. Wang BC, Hillman DE, Spielholz NI, et al. Neurological deficits and Nesacaine-CE- an effect of the anesthetic 2-chloroprocaine, or the antioxidant Na bisulfite? Anesth Analg 1984;63:445-7.
11. Ready LB, Plumer MH, Haschke RH, et al. Neurotoxicity of intrathecal local anesthetics in rabbits. Anesthesiology 1985;63:4:364-70.
12. Wang BC, Spielholz NI, Hillman DE, et al. Subarachnoid Na bisulfite (the antioxidand in Nesacaine) causes chronic neurologic deficit. Anesthesiology 1986:57:A194.
13. Tapia DP, Waxler BJ, Hursh D, Aldrete JA. Effects of Na bisulfite on Sprague Dawley rat sciatic nerve: A preliminary report. Reg Anesth 1990;15:Abst. 90.
14. Gissen AJ, Datta S, Lambert D. The chloroprocaine controversy I: A hypothesis to explain the neural complications of chloroprocaine epidural. Reg Anesth 1984;9:124-34.
15. Gissen AJ, Datta S, Lambert D. The chloroprocaine controversy. II Is chloroprocaine neurotoxic? Reg Anesth 1984;9:135-45.
16. Fibuch EE, Opper SE. Back pain following epidurally administered Nesacaine-MPF. Anesth Analg 1989;69:113-5.
17. Barsa J, Batra M, Fink BR, Sumi M. Comparative *in vivo* Study of Local Neurotoxicity of Lidocaine, Bupivacaine, 2-Chloroprocaine, and a Mixture of 2-Chloroprocaine and Bupivacaine. Anesth Analg 1982;61:12:961-7.
18. Kalichman MW, Powell HC, Reisner LS, et al. The role of 2-chloroprocainbe and Na bisulfate in rat sciatic nerve edema. J Neuropathol Exp Neurology1986;45:566-75.
19. Myers RR, Kalichman MW, Reisner LS, et al. Neurotoxicity of local anesthetics: Altered perineural permeability, edema and nerve fiber injury. Anesthesiology 1986;64:29-35.
20. Seravalli CP, Lear E, Cotrell JE. Cell membrane fusion by chloroprocaine. Anesth Analg 1984;63:985-90.
21. Tanigucgi M, Bollen AW, Drasner K. Na bisulfite, scapegoat for chloroprocaine neurotoxicity? Anesthesiology 2004;100:85-91.
22. Lambert DH, Strichartz GR. In defense of *in vitro* findings. Anesthesiology 2004;101:1246-7.

23. Moore DC. Labeling package insert: meaning by the FDA of not recommended, not indicated and off-label use. Anesthesiology 2006;104:104-6.
24. Horlocker TT, Wedel DJ. Local anesthetic toxicity-does product liability reflect the risk? Reg Anesth Pain Med 2002;27:562-7.
25. Myers RR, Olmarker K. Anatomy of DRG, intrathecal nerve roots and epidural nerves with emphasis on mechanisms of neurotoxicity. In: Spinal Drug Deliver, T.L. Yaksh (ed). Elsevier Science, Amsterdam. 1999;115-31.
26. Chestnut DH. Obstetric Anesthesia: principles and Practice. 3rd edition. Mosby, St. Louis. 2004:415.
27. Reynolds F, Speedy HM. The subdural space: the third place to go astray. Anaesthesia 1990;45:120-3.
28. Pan PH, Board TD, Owen TD, et al. Incidence and characteristics of failures in obstetrical neuraxial analgesia and anesthesia: a retrospective analysis of 19,259 deliveries. Int J Obstet Anesth 2004;13:227-33.
29. Balistieri PJ. Epidural chloroprocaine-standard of care for postpartum tubal ligation? Anesth Analg 2005;101:1241.
30. Halpern SH, Douglas MJ. Evidence-based obstetric anesthesia. Blackwell, Malden, MS. 2005;239-44.
31. Na KB, Kopacz DJ. Spinal CHLP solutions: density at 37 degrees C and titration. Anesth Analg 2004;98:70-4.
32. Yoos JR, Kopacz DJ. Spinal 2-CHLP for surgery: an initial 10 month experience. Anesth Analg 2005;100:553-8.
33. Smith KN, Kopacz DJ, McDonald SB. Spinal 2-CHLP: a dose ranging study and the effects of added epinephrine. Anesth Analg 2004;98:81-8.
34. Vath JS, Kopacz DJ. Spinal 2CHLP: the effect of added fentanyl. Anesth Analg 2004;98:89-94.
35. Warren DT, Kopacz DJ. Spinal 2CHLP: the effect of added dextrose. Anesth Analg 2004;98:95-101.
36. Davis BR, Kopacz DJ. Spinal 2_CHLP: the effect of added clonidine. Anesth Analg 2005;100:559-65.
37. Yoos JR, Kopacs DJ. Spinal 2-CHLP: a comparison with small dose bupivacaine in volunteers. Anesth Analg 2005;100:566-72.
38. Gonter AF, Kopacz DJ. Spinal 2-CHLP a comparison to procaine in volunteers. Anesth Analg 2005;100:573-9.
39. Kouri ME, Kopacz DJ. Spinal 2-CHLP: a comparison with lidocaine in volunteers. Anesth Analg 2004;98:70-4.
40. Casati A, Danelli G, Berti M, et al. Intrathecal 2-chloroprocaine for lower limb outpatient surgery: a prospective, randomized, double-blind, clinical evaluation. Anesth Analg 2006;103:234-8.
41. Casati A, Fanelli G, Danelli G, et al. Spinal anesthesia with lidocaine or preservative-free chloroprocaine for outpatient knee arthroscopy: A prospective, randomized, double blind comparison. Anesth Analg 2007;104:959-64.
42. Drasner K. Chloroprocaine spinal anesthesia: Back to the future. Anesth Analg 2005;100:549-52.
43. Palas TAR. 1% chloroprocaine for spinal anesthesia: an ideal local anesthetic drug for short surgical procedures? Reg Anesth Pain Med 2007;32:8.
44. Hejtmaneck M, Pollock JE. Spinal 2-chloroprocaine for outpatient surgery-experience with 600 anesthetics. ASRA Congress 2008, Abstract ID A-24.
45. Ruben SS. Retraction of 10 published articles in Anesthesia and Analgesia. Notice of Retraction 2009;109:1350.
46. Struys MMR, Fechner J, Schuttler J, Schilden H. Requested retraction of six studies on the PK/PD and tolerability of fospropofol. Anesth Analg 2010;110:1240.