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Influence of Local Anesthetic Solution on Postdural Puncture Headache

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A total of 2,511 patients who received spinal anesthesia for cesarean delivery were observed for the development of postdural puncture headache (PDPH); 804 patients received a mixture of tetracaine and procaine, 942 received bupivacaine–glucose, and 765 received lidocaine–glucose. They were observed for the development of PDPH for a minimum of 72 h. PDPH occurred in 9.54% of patients who received lidocaine–glucose during the first 36 h compared with 7.64% of patients who received bupivacaine–glucose and 5.85% of patients who received tetracaine–procaine. The differences between all groups was statistically significant. No differences were found in the percentage of patients who ultimately required epidural blood patch for relief of symptoms after 36 h. (Key words: Anesthesia, obstetric. Anesthetics, local: bupivacaine; lidocaine; tetracaine. Anesthetic techniques: spinal. Complications: headache.)

POSTDURAL PUNCTURE HEADACHE (PDPH) is one of the most commonly reported postoperative complications of spinal anesthesia.[1] The mechanism of the headache is thought to be a decrease in cerebrospinal fluid (CSF) pressure produced by leakage through the dural membrane at the needle puncture site. This lowered pressure in turn produces traction on intracerebral supporting structures and blood vessels and results in the sensation of headache.[2]

The incidence of this complication is increased when larger needles are used to perform the dural puncture and when the patient is poorly hydrated prior to or after the dural puncture.[3] The incidence of PDPH is higher in females than in males and decreases with advancing age. One of the patient groups found to be at highest risk for PDPH is parturients.[4]

The influence of the local anesthetic drug used to produce spinal anesthesia on the incidence of PDPH is not known. In 1956 Vandam and Dripps[5] reported on more than 10,000 spinal anesthetics performed by a variety of personnel at the University of Pennsylvania during 1948–1951. Their data suggested that the drug used as the spinal local anesthetic did not influence the incidence of PDPH. However, in that study all spinal needles were reused, the smallest needle size used was 24-G and most of the patients had their dural punctures performed with 16- to 22-G needles. The effect of needle size and condition probably would have obscured the contribution to the incidence of PDPH of the drug used. In addition, since the time of the Vandam and Dripps[5] study, several new drugs have been introduced for spinal anesthesia. Reusable spinal needles have virtually disappeared, and many other changes in technique have occurred.

In 1980 Hoffman and Schockenhoff[6] reported a retrospective review of 503 spinal anesthetics performed in a heterogeneous patient population undergoing many different operative procedures, and they noted that 4% mepivacaine with dextrose 10% was associated with an increased incidence of PDPH compared with that following 2% mepivacaine or 0.5% tetracaine without dextrose. To clarify the role of the local anesthetic and/or dextrose in the production of PDPH, we studied the influence of the local anesthetic drug on the incidence of PDPH in a population at high risk for PDPH.

Materials and Methods

We received approval from the Committee on Human Studies of the Brigham and Women's Hospital to conduct this study. We prospectively evaluated all patients (n = 2,511) who received spinal anesthesia for both elective and emergent cesarean delivery at the Brigham and Women's Hospital during the 34-month period from May 1984 to February 1987. All patients had midline dural punctures performed between L2 and L4 with a 26-G B-D™ disposable single-use spinal needle, by either residents with at least 8 months of previous anesthesia clinical training directly supervised by attending anesthesiologists or by attending anesthesiologists themselves. All spinal anesthetics were performed using disposable Travenol™ or Abbott™ spinal anesthesia kits, and the needles were inserted with the bevel of the needle parallel to the longitudinal axis of the spinal cord.

The patients received standardized doses (based on patient height) of spinal local anesthetic solutions.[7] These solutions were 5% lidocaine in 7.5% glucose, 0.75% bupivacaine in 8.25% glucose, or 1% tetracaine diluted with an equal volume of 10% procaine. The volume of injectate varied from 1.2 to 1.8 ml. The choice of local anesthetic solution was based only on the anticipated duration of the procedure based on previous experience with the sur-

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geon, with lidocaine being chosen for the surgeons with a history of rapid surgical procedures and tetracaine chosen for those with the history of longest surgical durations.

All patients received a minimum of 1,500 ml of lactated Ringer's solution prior to the dural puncture, and the intravenous (iv) infusion was continued until the patient was tolerating oral fluids well. The patients were allowed to ambulate freely after recovery from the block. Patients were seen daily by one of the authors (L.H.) during their hospital stay, and she noted the presence or absence of a headache of any sort. If a headache was reported, the patient was seen by an anesthesiologist and evaluated. If a patient was found to have a moderate or severe postural headache, with or without tinnitus, blurred vision, or nausea or vomiting, the presumptive diagnosis of PDPH was made. The persons initially evaluating the headache were unaware that a study was being performed to relate the selection of anesthetic drug with the incidence of PDPH and were unaware of the potential significance of the local anesthetic used for the procedure. The type and dosage of local anesthetic was required to be included on the anesthetic record for ethical and legal reasons.

If the patient was found to have PDPH, as diagnosed by the presence of the above criteria, she received conservative therapy for at least 48 h, consisting of hydration, bed rest, and oral analgesics. If this regimen failed to relieve the headache, and if the patient agreed, an epidural blood patch was performed. The number of patients diagnosed as having PDPH and the number of patients who had epidural blood patches recommended and performed in each of the drug groups were recorded. Contingency table analysis was performed on the nonparametric data as a test of statistical significance, with a significance level set at 97.5%. Multiple analysis of variance (ANOVA) was performed on parametric data.

Results

There was no difference in patient ASA Physical Status, height, weight, gravidity, or parity between any of the local anesthetic groups. The amount of iv fluid administered in the first 36 h or the time to first ambulation did not differ significantly among the groups. The length of time spent in the recovery room was longer in the patients who received tetracaine–procaine (3.2 ± 1.2 h) than in patients who received bupivacaine (2.8 ± 1.1) or lidocaine (2.2 ± .6 h). However, these differences were not statistically significant ($P = 0.16$).

The incidence of non-PDPH did not differ between the groups (table 1). Although the drug selection was made on the basis of anticipated duration of the procedures, the actual mean duration of the procedures did not differ significantly among the dosage groups (47.3 ± 13 min in the lidocaine group, 58.3 ± 12.1 min in the bupivacaine group, and 54.3 ± 15.2 min in the tetracaine group). There was no difference in the incidence of emergency cesarean deliveries among the three groups. In the tetracaine–procaine group 22.1% of patients were in labor, in the lidocaine group 19.3% of patients were in labor, and in the bupivacaine group 24.2% of patients were in labor at the time of cesarean delivery (NS). All patients were ASA Physical Status 1 or 2. There was no significant difference in the mean number of recorded attempts before successful lumbar puncture in the three groups.

TABLE 1. Incidence of Headache, PDPH, and Epidural Blood Patch in Patients after Cesarean Delivery

Local Anesthetic	N	Headaches	% Headache	PDPH	% PDPH	% Blood Patch
Tetracaine–procaine	804	97	12.1	47	5.85	1.6
Bupivacaine–glucose	942	129	14.2	84	8.81*	1.7
Lidocaine–glucose	765	120	15.7	73	9.54*	1.6

* $P < 0.025$, compared with patients receiving tetracaine–procaine.

The percentage of patients developing PDPH within 36 h following lumbar puncture who received tetracaine–procaine, bupivacaine–glucose, or lidocaine–glucose was 5.85%, 8.12%, and 9.54%, respectively (table 1). The incidence of PDPH in the patients receiving lidocaine–glucose or bupivacaine–glucose was significantly greater than in patients receiving tetracaine–procaine ($P = 0.0059$). There was no difference between the lidocaine and the bupivacaine groups ($P = 0.5979$). There was no difference in the overall incidence of PDPH in the various drug groups whether the patient was in labor (emergent cesarean delivery) or not in labor (elective cesarean delivery), and there was no correlation between the incidence of PDPH with the total dose of local anesthetic agent used or the patient height (from which the total dose was determined).

The percentage of patients developing a headache that did not meet our criteria for PDPH within 36 h following lumbar puncture who received tetracaine–procaine, bupivacaine–glucose, or lidocaine–glucose was 9.4%, 8.3%, and 7.8% respectively (table 1). If the patients experiencing non-PDPH are included in the data analysis, the incidence of headache is still significantly higher in the patients receiving lidocaine–glucose and bupivacaine–glucose ($P = 0.025$ and $P = 0.023$, respectively) than in those receiving tetracaine–procaine.

Figure 1 demonstrates the cumulative percentage of patients reporting symptoms consistent with PDPH in each drug group during the 48 h following dural puncture. The percentage of patients reporting a PDPH was significantly higher in both the bupivacaine and the lidocaine groups than in the tetracaine group at all measurement intervals except at 2 and 48 h following dural

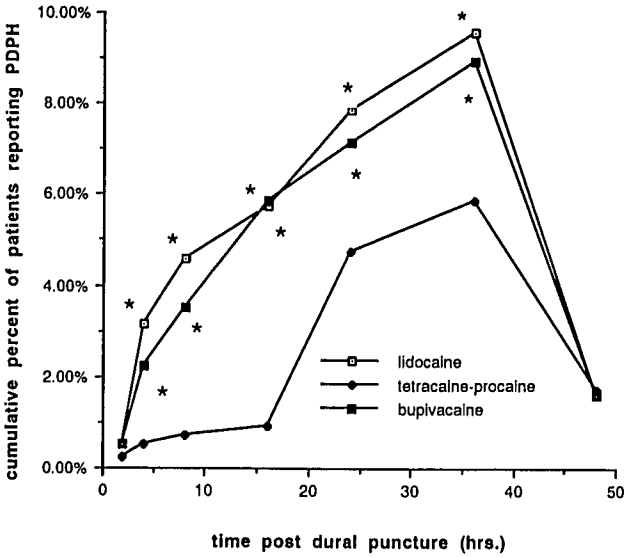

FIG. 1. The cumulative percentage of patients reporting symptoms of PDPH for 48 h following spinal anesthesia for cesarean delivery.

puncture. This difference was not attributable to differences in time of beginning ambulation. Although one might expect the longer-acting local anesthetics to significantly delay ambulation, the mean time to ambulation in all three groups did not differ significantly. In the lidocaine group the mean time to ambulation was 8.5 ± 2.1 h, in the bupivacaine group 9.1 ± 3.2 h, and in the tetracaine–procaine group 10.1 + 4.2 h ($P = 0.25$ and $P = 0.65$, respectively, compared with tetracaine–procaine). There was no difference in the percentage of patients reporting PDPH at any time between the lidocaine and bupivacaine groups.

It is difficult to assess the duration of PDPH in this study because all patients with a persistent headache were offered blood patching 48 h after the onset of the headache. However, figure 1 shows the percentage of patients reporting PDPH at varying times following dural puncture. It can be seen that the patients in the lidocaine and bupivacaine groups reported symptoms of PDPH (as defined) significantly more frequently ($P < 0.025$) than patients in the tetracaine–procaine group during the period of time from 4 to 36 h, but do not differ at 48 h.

Despite the increased incidence of headache in patients receiving lidocaine–glucose and bupivacaine–glucose in the first 36 h following the lumbar puncture, we found no difference in the number of patients who ultimately received epidural blood patches for treatment of their headaches in any of the three groups (1.6% in patients receiving tetracaine–procaine, 1.7% in patients receiving bupivacaine–glucose, and 1.6% in patients receiving lidocaine–glucose). There was no difference in the number of patients with the presumptive diagnosis of PDPH who initially refused blood patching. Three patients in the Tetracaine–procaine group, two in the lidocaine group, and four in the tetracaine group initially refused blood patches (at 36–48 h post lumbar puncture) and were discharged from the hospital with residual headache. All but one of these patients (who had received tetracaine–procaine) subsequently received epidural blood patches as outpatients and were included in the statistical analysis as having received blood patches. However, the exclusion of these patients from the analysis does not alter the results. According to our normal protocol, all blood patches were performed a minimum of 48 h after the dural puncture. There was no statistically significant difference in the incidence or time of performance of epidural blood patch between any of the drug groups.

Discussion

The results of this study suggest that the local anesthetic drug used to produce spinal anesthesia can influence the incidence of postoperative PDPH in patients who receive spinal anesthesia for cesarean delivery. In our study we found that patients who received lidocaine–glucose or bupivacaine–glucose had a significantly higher incidence of PDPH in the first 36 h postpuncture, whereas those who received a solution containing tetracaine and procaine had the lowest incidence of PDPH. We also found that the local anesthetic did not appear to influence the percentage of patients who ultimately required epidural blood patching for control of their PDPH. In addition, we have observed an incidence of PDPH requiring treatment (blood patching) of 1.6–1.7% following lumbar puncture with 26-G needles regardless of the drug chosen for spinal anesthesia.

These observations suggest that there may be at least two different mechanisms involved in the production of the syndrome of PDPH. The headache that first appeared following lumbar puncture for spinal anesthesia in the patients in our study was an acute, postural, transient headache, the incidence of which was influenced by the drug selected to produce spinal anesthesia. This PDPH occurred in approximately 5–10% of patients in our study, was occasionally severe, but was usually of rather short duration, ranging from 24–36 h. The second phase, usually occurring after 24–36 h, may become chronic.[3] The mechanism of the second phase is probably CSF loss through the dural puncture site. This leakage was uninfluenced by the drug selected, had an approximate incidence of 1.6–1.7%, and was treated successfully by epidural injections of autologous blood.

The reason that significant differences in the incidence of "immediate" PDPH are exhibited by the drugs used in our study is presently unclear. One possibility is that the difference is due to the different chemical structures

of the two groups of local anesthetics used in this study. In 1956, Vandam[4] stated that it was unlikely that any drug injected into the lumbar CSF would reach intracranial structures and, therefore, the local anesthetic solutions could not play a role in the production of headache. In 1962 Reiselbach *et al.* showed that rostral spread of several drugs, including lidocaine, could be demonstrated in monkeys following lumbar injection.[8] More recently, studies of intrathecal opioids have revealed that significant amounts of drugs injected into the lumbar CSF are detectable in intracerebral structures for up to 24 h.[9,10] The duration of persistence of drugs in CSF appears to be inversely proportional to lipid solubility and directly proportional to the amount of protein binding.[11] Of the drugs employed in the study, lidocaine exhibits the lowest lipid solubility and bupivacaine the highest protein binding, and these drugs should be expected to persist in the CSF in low concentrations for longer periods of time than tetracaine based on these physical properties. Amide local anesthetics, like lidocaine and bupivacaine, might also be expected to persist longer in the CSF than esters because the CSF is known to possess significant esterase activity.[12] Both of these pharmacologic properties make it likely that, of the three drug combinations tested, lidocaine and bupivacaine are most likely to produce low concentrations of drug within the intracranial CSF for a significant period of time. It is known that low concentrations of lidocaine and bupivacaine have vasoconstrictor properties,[13] whereas ester local anesthetics (*e.g.*, procaine, tetracaine) have been described as having vasodilatory properties.[14] We postulate that the low concentrations of lidocaine and bupivacaine that are probably present in intracranial CSF following spinal anesthesia could produce a transient headache by producing transient constriction of intracranial blood vessels, possibly followed by a reactive hyperemia. This mechanism may explain the effectiveness of large iv doses of caffeine benzoate[15] or nonsteroidal antiinflammatory drugs[16] at reducing the severity of PDPH in its early phases. Obviously, studies to ascertain the long-term pharmacokinetics and pharmacodynamics of local anesthetics in CSF following spinal anesthesia would be necessary to confirm or deny this possibility.

A second possible explanation for our findings lies in the observation that the higher incidences of PDPH, both in our prospective study and in another retrospective study,[6] were associated with solutions that contained glucose. Several mechanisms may be proposed by which glucose could contribute to the sensation of headache; 7.5% glucose, for example, represents a glucose concentration of 75 mg/ml, or in the units commonly used to express CSF glucose, 7,500 mg/dl. When this is injected into the lumbar CSF, it should rapidly equilibrate with the approximately 100–150 ml of CSF, which would produce a transient increase of 75 mg/dl in the normal CSF glucose concentration. This could have either osmotic effects or direct irritant effects on cerebral or meningeal structures, producing the sensation of headache. Several published studies[17,18] of hyperbaric *versus* isobaric local anesthetic mixtures have reported a higher incidence of PDPH when higher glucose concentrations were employed. Recently, Wilder-Smith and Gurtner,[19] in a study of 320 patients, have also remarked on the prevalence of an "immediate, nontypical" PDPH in patients who received hyperbaric lidocaine as a spinal anesthetic agent, which they did not observe with isobaric tetracaine.

Finally, because the assignment of patients into study groups was neither random nor completely blinded, but based on the estimated length of the procedure, it is conceivable that this method of selection introduced an unknown bias into the study groups. One must allow the possibility that in some fashion, the duration of the procedure affected the incidence of PDPH. However, the actual durations of the procedures did not differ significantly among the three groups; thus, the likelihood of bias from this method of selection appears to be small. The demographics that were collected for all members of the study were limited (patient height, weight, gravidity, parity, incidence of labor and emergency cesarean section, ASA Physical Status), but we believe that these patient groups were indeed comparable. Although we have no reason to suspect that the groups did differ from one another, this is a flaw in the experimental design. Also, we did not make the drug selection absolutely blind to the evaluator of the headache. The information was not explicitly given to the evaluator but was required by our Investigational Review Committee to be present on the anesthesia record for ethical and legal reasons. In addition, we did not inform the evaluators that the patients were being studied for the relationship between local anesthetic and PDPH in an attempt to further minimize this potential bias and to decrease the likelihood of changing practice merely by announcing such a study, the so-called Hawthorne effect.[20] We also believe that the strict criteria we used to diagnose a PDPH and the inclusion of large numbers of patients in each group should minimize the impact of any residual bias attributable to the nonrandom nature of patient assignment. Further studies should be performed to confirm or deny the validity of our admittedly preliminary observations.

In summary, our observations suggest that there are probably at least two phases of PDPH. The first phase has an early onset and short duration (approximately 24 h) and has an incidence that varies with the drug mixture used and at present is produced by an unknown mechanism. The existence of this type of headache may explain the relative ineffectiveness of epidural blood patches in the first 36 h following lumbar puncture[3] because EBP would be expected to have little or no effect on this type

of PDPH. The second phase is unrelated to the local anesthetic agent, is probably due to leakage of CSF from the dural puncture, and is longer-lasting, more severe, and responds well to administration of an epidural blood patch. Further studies should be performed to test these observations in different patient populations, and these studies should be designed to elucidate the mechanism of these differences. One important first step would be to compare the incidence, severity, and duration of headache with one drug, with or without glucose, to elucidate the role of glucose. Second, animal studies should be performed to further delineate the intracranial distribution and pharmacokinetics of lumbar subarachnoid injections of local anesthetics. It is our hope that others will utilize these observations for a better understanding of the mechanisms of PDPH and possibly find methods to further reduce its incidence.

References

1. Bonica JJ: Principles and Practice of Obstetric Analgesia and Anesthesia. Philadelphia, FA Davis, 1972, p 102
2. Kunkle EC, Ray BS, Wolff HG: Experimental studies on headache: Analysis of the headache associated with changes in intracranial pressure. Arch Neurol Psychiatry 49:323–358, 1943
3. Poukilla E: The problem of post-spinal headache. Ann Chir Gynaecol 73:139–142, 1984
4. Vandam LD: Neurologic sequelae of spinal and epidural anesthesia. Int Anesthesiol Clin 24:231–255, 1986
5. Vandam LD, Dripps RD: Long-term follow up of patients who received 10098 spinal anesthetics. JAMA 161:586–597, 1956
6. Hoffman P, Schockenhoff B: Headache after spinal analgesia with reference to the type of analgesic agent used. Anasth Intensivther Notfallmed 15:416–422, 1980
7. Chantigian RC, Datta S, Burger GA, Naulty JS, Lanmbert DH, Ostheimer GW: Anesthesia for cesarean delivery using spinal anesthesia. Tetracaine vs tetracaine and procaine. Reg Anaesth 9:195–199, 1984
8. Reiselbach RE, DiChiro G, Freireich EG, Rall DP: Subarachnoid distribution of drugs after lumbar injection. N Engl J Med 267: 1273–1278, 1962
9. Downing JW, Williams V, Hascke R, Porte D, Woods S, Fogel K, Horn J: Rostral spread of epidural morphine (letter). Anesth Analg 63:375–376, 1984
10. Atchjison S, Durant PAC, Yaksh TL: Cardiorespiratory effects and kinetics of intrathecally injected D-Ala2-D-Leu5-enkephalin and morphine in unanesthetized dogs. ANESTHESIOLOGY 65: 609–616, 1986
11. Gustafsson LL, Post C, Edvardsen B, Ramsay CH: Distribution of morphine and meperidine after intrathecal administration in rat and mouse. ANESTHESIOLOGY 63:483–489, 1985
12. Scarsella G, Toschi G, Bareggi SR, Giacobini E: Molecular forms of cholinesterases in cerebrospinal fluid, blood plasma, and brain tissue. J Neurosci Res 4:19–24, 1979
13. Johns RA, DiFazio CA, Longnecker DE: Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. ANESTHESIOLOGY 62:141–144, 1985
14. Willatts DG, Reynolds F: Comparison of the vasoactivity of amide and ester local anaesthetics. An intradermal study. Br J Anaesth 57:1006–1011, 1985
15. Jarvis AP, Greenawalt JW, Fagraeus L: Intravenous caffeine for postdural puncture headache. Anesth Analg 65:316–317, 1986
16. Kannisto K, Kataja M: The prevention of headache following spinal anesthesia. Ann Chir Gynaecol 70:107–111, 1981
17. Axelsson K, Widman B: Clinical significance of specific gravity of spinal anesthetic agents. Acta Anaesthesiol Scand 23:427–434, 1979
18. Chambers WA, Edstrom HH, Scott DB: Effect of baricity on spinal anesthesia with bupivacaine. Br J Anaesth 53:279–282, 1981
19. Wilder-Smith OH, Gurtner T: Headache following spinal anesthesia: Also a problem of the local anesthetic used? Reg Anaesth 10:59–64, 1987
20. Murray M, Swan AV, Kiryluk S, Clarke GC: The Hawthorne effect in the measurement of adolescent smoking. J Epidemiol Community Health 42:304–306, 1988