

Diagnostic Cohort Study Comparing the Accuracy of PDPH Trial Criteria vs International Headache Society Criteria for Post-epidural PDPH

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INTRODUCTION

- In obstetric anesthesia practice, epidural needles, rather than spinal needles, represent the most important source of post dural puncture headache (PE-PDPH).
- Despite the important differences that exist between epidural and spinal procedures and their likely impact on PE-PDPH, these differences have yet to be meaningfully addressed by International Headache Society (IHS) criteria for PDPH diagnosis (see Fig. 1). They include:
 - 1) High incidence of unrecognized dural sac injury during epidural needle placement
 - 2) Variability in dural injury during accidental dural puncture which may effect PE-PDPH onset and severity
 - 3) Potential diagnostic confounding by pneumocephalus from LOR to air techniques
 - 4) Continued omission of *postural neckache without headache* as a PDPH variant despite literature which supports its inclusion
- Diagnostic criteria for PE-PDPH were developed to address these issues and used as the primary outcome in the Canadian Multicentre PDPH Trial (CMPT; PDPH Trial Criteria, Fig. 1). This Trial compared the incidence of PE-PDPH within the first 14 days of labor epidural placement in 1081 women randomized to receive small (19g) vs large (16-18g) Tuohy-type needles. All women were followed forward for possible PE-PDPH over 14 days after epidural placement as measured by a Triage Test (i.e., development of a “bothersome headache or neckache that worsened with movement of any kind” during standardized follow). PE-PDPH was diagnosed using PDPH Trial Criteria (primary outcome) and IHS ICHD-11 Criteria (secondary outcome) by a blinded independent adjudicating body of three senior anesthesiologists matched 1:1 with an expert headache specialist neurologist for diagnosis.
- An embedded diagnostic study in the Trial permitted comparison of the accuracy of PDPH Trial Criteria with IHS ICHD-11 Criteria $\leq$ 14 days after epidural placement against an Umpire Reference Test, an independent, blinded diagnosis of symptoms consistent with CSF leakage made by a second expert headache specialist/neurologist based on standardized long-term patient follow up (to symptom resolution, maximum 1 year) and clinical experience. Trial findings suggested the diagnostic performance of PDPH Trial Criteria was superior to IHS ICHD-11 Criteria for PE-PDPH (see Fig. 2).
- IHS ICHD-3 Criteria [1] were introduced shortly after conclusion of the CMPT and are now advocated for diagnosis of PDPH. This retrospective cohort study used case report forms from women identified with possible PE-PDPH in the Trial to compare the diagnostic accuracy of PDPH Trial Criteria versus IHS ICHD-3 Criteria against the same Umpire Reference Test.**
- Primary Research Question:** What is the performance of PDPH Trial Criteria versus IHS ICHD-3 Criteria for PE-PDPH diagnosis within the first 14 days of labor epidural placement when assessed against the Umpire Reference Test (long-term follow up/expert opinion by a headache specialist/neurologist) used in the CMPT?
- Secondary Research Questions:** How do PDPH Trial Criteria compare with IHS ICHD-11 Criteria for PE-PDPH diagnosis based on the Umpire Reference Test? How do diagnoses based on clinical experience of each adjudicator compare with the Umpire Reference Test? How do adjudicators' recommendations for Epidural Blood Patch (EBP) in true positive cases of PE-PDPH compared within 14 days of epidural placement?

Figure 2: CMPT Diagnostic Performance of PDPH Criteria vs IHS ICHD-11 Criteria against an Umpire Reference Test

Diagnostic Performance Metric	Criteria	
	PDPH Trial Criteria	IHS ICHD-11
Sensitivity	0.71	0.35
Specificity	0.98	0.97
AUC (95% CI)	0.85 (0.75, 0.94)	0.66 (0.54, 0.78)
LR+	36	11
LR-	0.30	0.67
PPV	0.88	0.69
NPV	0.94	0.88
Kappa	0.93*	0.70*

METHODS

- After REB approval, case report forms for 184 women identified with a positive triage test for possible PE-PDPH within 14 days of epidural placement in the CMPT were assessed using three Index Tests and clinical experience of Day 14 adjudicators (Fig. 3 Study Flow Diagram, Fig. 4 Demographic Table n=184).
- PE-PDPH diagnoses were made by six mid-career to senior staff obstetric/regional Anesthesiologists randomly allocated to adjudicate each case in fixed pairs using either PDPH Trial Criteria, IHS ICHD-11 criteria, or IHS ICHD-3 Criteria. During evaluations, adjudicators first independently assessed each case for PE-PDPH using their assigned diagnostic criteria. Adjudicators were blinded to diagnoses made by their adjudicating partner and other adjudicators, as well as the needle used during epidural placement. First pass agreement for PE-PDPH was assessed between adjudicators for each set of diagnostic criteria (kappa statistic). When discordance was found, the case was re-reviewed and a consensus diagnosis of PE-PDPH (yes/no) was made.
- The same anesthesiologist assessors, as well as a second independent, blinded headache specialist/neurologist, also rated each case for PE-PDPH (yes/no) within the first 14 days of epidural insertion based on their clinical experience. Assessors identified cases they believed should have been recommended/received an EBP (regardless of what actually happened in the Trial), as well as cases they believed warranted > 14 days of follow up and/or medical imaging as part of PE-PDPH diagnosis.
- Diagnostic performance of each Index test was assessed against an Umpire Reference Test using independent, blinded assessments made by a second expert headache specialist/neurologist who assessed each case for symptoms consistent with CSF leakage based on long-term follow up (symptom resolution, maximum 1 year) from the Trial.
- Measures of Diagnostic Performance were: a) Sensitivity, b) Specificity, c) Area under the Curve (AUC) for Receiver Operating Characteristic (ROC) curves [2], d) Likelihood Ratios (LR), and e) Positive and negative predictive values.

Figure 1: PDPH Trial Criteria for PE-PDPH IHS ICHD-11 and IHS ICHD-3 Criteria for PDPH

PDPH Trial Diagnostic Criteria

Description: Diagnosis of PE-PDPH using PDPH Trial Criteria requires a “yes” for questions 1 through 5. Rarely, PDPH symptoms may be REVERSE postural. Note that unrecognized dural injury with the epidural needle is a common source of PE-PDPH; recognized or suspected dural injury is not required using PDPH Trial Criteria. Patients with PE-PDPH may have one or more of the symptoms found in criteria 7; these are considered supportive but not necessary for diagnosis. Development of additional focal neurologic symptoms/signs are not consistent with uncomplicated PE-PDPH.

Diagnostic Criteria

- 1) Was this a **new** headache and/or neckache which started within the first 14 days after epidural needle insertion?
- 2) Did the headache and/or neckache persist for at least 24 hours after epidural needle insertion?
- 3) Were the headache and/or neckache symptoms postural?
- 4) Did they start or worsen within 15 minutes of sitting or standing?
- 5) Did they improve or completely go away within 15 minutes of lying down?
- 6) Was there a recognized or suspected dural sac puncture with the epidural needle?
- 7) Did the patient develop any of the following symptoms (check all that apply)?
 - Visual (e.g., diplopia, photophobia, blurred vision),
 - Auditory (e.g., tinnitus, muffled hearing),
 - Vestibular (e.g., dizziness, balance, vertigo, difficulties concentrating),
 - Nausea/vomiting

Did this patient have PE-PDPH based on PDPH Trial Criteria?

IHS ICHD-11 Criteria for PDPH

Diagnostic Criteria for 7.2.1: Post-dural (post-lumbar) puncture headache

A. Headache that worsens within 15 minutes after sitting or standing and improves within 15 minutes after lying, with at least one of the following and fulfilling criteria C and D: 1) neck stiffness; 2) tinnitus; 3) hypacusia; 4) photophobia; and 5) nausea
B. Dural puncture has been performed
C. Headache develops within 5 days after dural puncture
D. Headache resolves within either: a) spontaneously within 1 week; or b) within 48 hours after effective treatment of the spinal fluid leak (usually by EBP)
Note: In 95% of cases this is so. When headache persists, causation is in doubt.

Did this patient have PDPH based on IHS ICHD-11 Criteria?

IHS ICHD-3 Criteria for PDPH

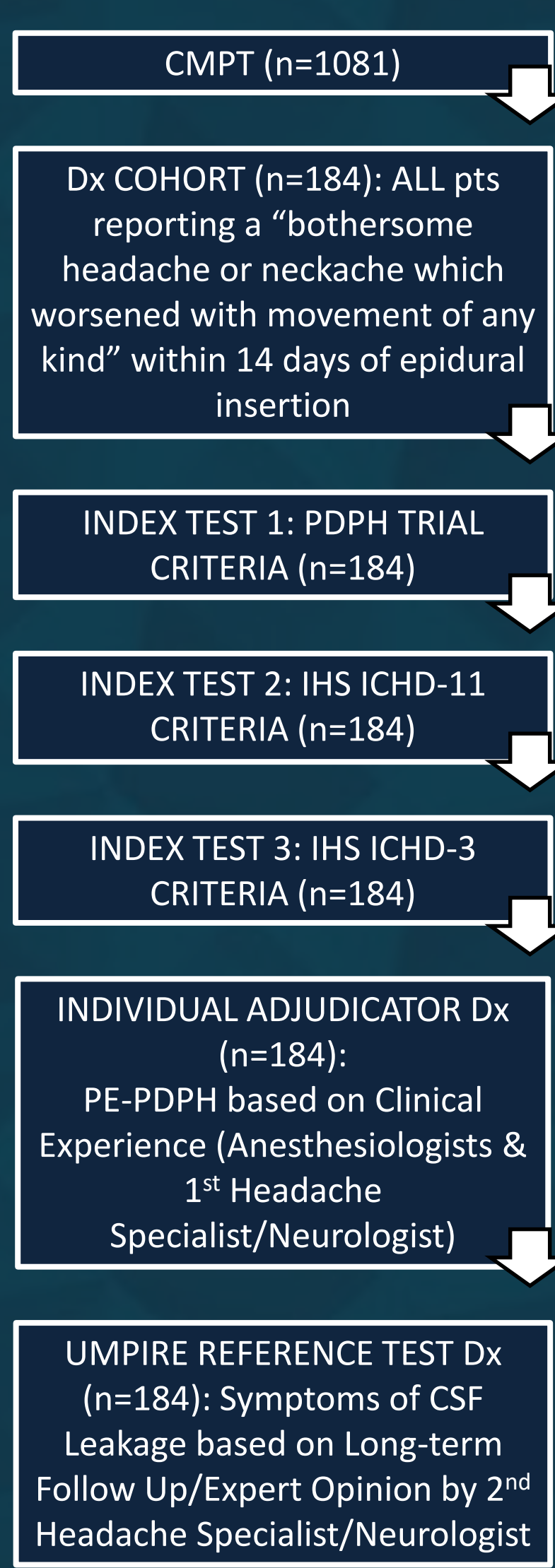
Description: Headache occurring within 5 days of a lumbar puncture, caused by CSF leakage through the dural puncture. It is usually accompanied by neck stiffness and/or subjective hearing symptoms. It remits spontaneously within 2 weeks, or after sealing of the leak with autologous EBP.

Diagnostic Criteria for 7.2.1: Post-dural puncture headache

A. Headache fulfilling criteria for 7.2 Headache attributed to low CSF pressure, and criterion C below
B. Dural puncture has been performed
C. Headache has developed within 5 days of the dural puncture
D. Not better accounted for by another ICHD-3 diagnosis.
Note: Independent risk factors for 7.2.1 have recently been demonstrated: female gender, age between 31 and 50 years, a previous history of 7.2.1 and orientation of the needle bevel perpendicular to the long axis of the spinal column at the time of the dural puncture.

Did this patient have PDPH based on IHS ICHD-3 Criteria?

Figure 3: Study Flow Diagram Retrospective Diagnostic Cohort Study



RESULTS

- Thirty-one out of 1081 women (2.9%) women were diagnosed with PE-PDPH by the Umpire Reference Test (see Fig. 5 for characteristics of PE-PDPH cases and Fig. 6 for diagnostic performance of each set of criteria).
 - First pass agreement between adjudicators was **substantial** for PDPH Trial Criteria (kappa 0.62 $p < .001$) vs **fair** for IHS ICHD-11 (kappa 0.26, $p < .001$) and IHS ICHD-3 (kappa =0.26, $p < .001$).
 - **PDPH Trial Criteria were more sensitive for PE-PDPH** (48%, 15/31) compared to IHS ICHD-11 (13%, 4/31) and IHS ICHD-3 (32%, 10/31); **all three diagnostic criteria showed high specificity (98-99%)**.
 - Overall diagnostic accuracy for **PDPH Trial Criteria was good to acceptable** (AUC 0.73, 95% CI [0.64, 0.82]), **unacceptable for IHS ICHD-11** (AUC 0.56, 95% CI [0.44, 0.68]) and **low for IHS ICHD-3 Criteria** (AUC 0.66, 95% CI [0.57, 0.74]).
- Independent agreement between adjudicators' recommendations for EBP in “true positive” cases (based on adjudicator consensus and the Umpire Reference Test) varied considerably depending on the diagnostic criteria used (see Fig. 7).
- Adjudicators using PDPH Trial Criteria identified two cases (14%, 2/14) they believed required > 14 days follow up and one case (7%, 1/15) for medical imaging while IHS Criteria identified no cases for either. The neurologist assessing diagnoses within 14 days of epidural placement identified one case (4.8%, 1/21) which required follow up > 14 days and 11 cases (50%, 11/22) where they believed medical imaging was warranted.
- The lower sensitivity of IHS Criteria ICHD-11 and ICHD-3 resulted in a large proportion of missed cases of PE-PDPH with ICHD-11 missing 27 cases (87%, 27/31) and ICHD-3 missing 21 cases (68%, 21/31) within the first 14 days of epidural placement, based on the Umpire Reference Test. 50% of the missed cases reported symptoms beyond 14 days after epidural insertion with average pain ratings of 6-7/10.
- Over half of cases of PE-PDPH that were missed by all diagnostic criteria 56% (15/27) reported bothersome PDPH-related symptoms beyond 14 days; about a third (33%, 8/27) of women reported having PDPH-related symptoms up to 13 weeks post epidural.

Figure 4: Demographic Information for Women with a Positive Triage Test (n=184)

Patient Characteristics	Small epidural needle (n=87)	Large epidural needle (n=97)
Age (years) Mean (SD)	32.0 (4.8)	32.1 (5.2)
BMI Mean (SD)	29.0 (4.4)	28.6 (4.5)
Parity, % Primiparous	63.2% (55/87)	60.8% (59/97)
Gestational Age in weeks Mean (SD)	39.7 (1.3)	39.6 (1.2)
Cervical Dilation (cm) @ Epidural Insertion, Mean (SD)	3.3 (1.3)	3.4 (1.4)
Delivery Mode		
SVD	55.2% (48/87)	66.0% (64/97)
Forceps/vacuum	23% (20/87)	11.3% (11/97)
C-section	21.8% (19/87)	22.7% (22/97)
Pushed? % YES	82.8% (72/87)	82.5% (80/97)
Minutes Pushing, Median (IQR)	35.0 (16.3, 90.0)	45.0 (16.3, 90.0)
Migraine Headache	25.3% (22/87)	20.6% (20/97)
Tension Headache	43.7% (38/87)	29.9% (29/97)
Sinus Headache	11.5% (10/87)	15.5% (15/97)
History of Spinal Headache	1.1% (1/87)	0% (0/97)
History of Meningitis	0% (0/87)	0% (0/97)
Neuraxial Morphine Used (% Yes)	28.7% (25/87)	25.8% (25/96)
LOR Technique		
NS Only	66.7% (58/87)	58.8% (57/97)
Air Only	16.1% (14/87)	20.6% (20/97)
Mixed NS/Air	17.2% (15/87)	20.6 (20/97)
Overall Incidence Dural Injury (via Epidural Needle, CSF per Catheter or IT Uptake of Drugs), Includes During Initial and Replacement Procedures		
Yes	2.3% (2/87)	2.1% (2/97)
Maybe	2	1
CSE Used	0	0
Spinal Anesthesia	0	1
PDPH Dx by Any Criteria in Replacement Cases Using CSE or Spinal Anesthesia	0	0

- PDPH Trial Criteria demonstrated overall superior diagnostic performance for PE-PDPH (AUC 0.73, 95% CI [0.64, 0.82]) compared with IHS ICHD-3 (AUC 0.66, 95% CI [0.57, 0.74]) and IHS ICHD-11 Criteria (AUC 0.56, 95% CI [0.44, 0.68]) during the first 14 days after labour epidural insertion compared with the Umpire Reference Test. This is consistent with CMPT findings from the embedded diagnostic study comparing ICHD-11 Criteria to the PDPH Trial Criteria using very senior, anesthesiologist expert adjudicators.
- Similarly, both studies showed that interrater agreement was better for PDPH Trial Criteria when compared with either set of IHS Criteria.
- PDPH Trial Criteria also demonstrated higher sensitivity than both IHS ICHD-3 and ICHD-11 Criteria, with similarly high specificity. These findings are consistent with our original comparison of the diagnostic accuracy of PDPH Trial Criteria with IHS ICHD-11 criteria for PE-PDPH against the same Umpire Reference Test in the CMPT.
- Although IHS ICHD-3 criteria clearly outperformed IHS ICHD-11 Criteria, PDPH Trial Criteria showed overall better performance suggesting that these criteria are preferred as part of development of a new diagnostic pathway for PE-PDPH.
- Long-term follow up of cases identified by the Triage Test showed that a large number of women developed PE-PDPH beyond five days after epidural insertion suggesting that a diagnostic window of 14 days is preferable. Similarly, many women continued to experience PE-PDPH related symptoms longer than 14 days after epidural insertion suggesting longer term follow up of these women is required.
- Lastly, little consensus (50-100%) was found between headache specialist/neurologist and anesthesiologist adjudicators for EBP recommendations for true positive cases of PE-PDPH based on the Umpire Reference Test. This suggests that an individualized approach to clinical care is being used and further research is required.

DISCUSSION

Figure 5: PE-PDPH Characteristics Based on the Umpire Reference Test (n=31)

Characteristic	Result	Note: 16% (1/6) pts diagnosed positive had a neckache but NO headache sxs
Postural H/A, Neckache + Assoc Sxs	42% (13/31)	
Postural H/A + Assoc Sxs (no neck)	16% (5/31)	
Postural H/A, Neckache (no Assoc Sxs)	13% (4/31)	
Postural H/A only	13% (4/31)	
Postural Neckache only*	13% (4/31)	Similar worst pain scores
Postural Neckache with Assoc Sxs (no headache)*	3% (1/31)	
Worst Pain Scores for all Cohort Pts $\leq$ 14 Days/Pre EBP (VAS) (Median, IQR)*	7 (6,9)	Postural neckache only
Postural Neckache only: Worst Pain Scores (n=5/31) (Median, IQR)	6 (3,9) (2/5 pts with Worst Pain Scores $\geq$ 7) (7.5/10 + 10/10)	
# EBP Recommended/Received	8/6 (1 patient had 2 EBP's)	Postural neckache only
Postural Neckache only pts: Recognized Dural Puncture	20% (1/5)	
EBP Received/Recommended/Responsive to EBP	20% (1/5)	

Figure 6: Diagnostic Performance of PDPH Trial Criteria vs IHS vs Clinical Experience for PE-PDPH within 14 Days of Epidural Insertion

Dx Performance	Criteria			Clinical Diagnosis						
	PDPH Trial	IHS ICHD-11	IHS ICHD-3	Adj'r 1	Adj'r 2	Adj'r 3	Adj'r 4	Ajd'r 5	Ajd'r 6	Headache specialist/ neurologist 1
Sensitivity	0.48	0.13	0.32	0.45	0.48	0.65	0.35	0.58	0.52	0.71
Specificity	0.98	0.99	0.99	0.99	0.99	0.95	1	0.97	0.95	0.73
AUC (95% CI)	0.73 (0.64, 0.82)	0.56 (0.44, 0.68)	0.66 (0.57, 0.74)	0.76 (0.64, 0.87)	0.68 (0.56, 0.80)	0.80 (0.70, 0.91)	0.68 (0.56, 0.80)	0.77 (0.66, 0.89)	0.74 (0.62, 0.85)	0.72 (0.62, 0.82)
LR+	24	20	32	35	37	14	NA	18	11	3
LR-	0.53	0.80	0.69	0.55	0.52	0.37	0.65	0.43	0.91	0.40
PPV	0.83	0.80	0.91	0.88	0.88	0.74	1	0.78	0.70	0.34
NPV	0.90	0.85	0.88	0.90	0.90	0.37	0.88	0.92	0.91	0.93
Kappa	0.62*	0.26*	0.26*	0.54	0.57	0.63	0.48	0.61	0.52	0.31

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References

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- 2) Mandrekar, JN. Receiver operating characteristic curve in diagnostic test assessment. *J Thorac Oncol*. 2010;5(9):1315-1316.