

Post-dural puncture headache incidence after cerebrospinal fluid aspiration. A prospective observational study

Incidência de cefaleia pós-punção dural após aspiração do líquido cefalorraquidiano. Um estudo observacional prospectivo

Rodrigo Tomazini MARTINS^{1,2}, Barbara TOSON³, Ricardo Krause Martinez de SOUZA^{1,4}, Pedro Andre KOWACS¹

ABSTRACT

Background: Post-dural puncture headache (PDPH) is an iatrogenic condition following lumbar puncture (LP). Incidence is variable and often associated with young females. Technical features of the procedure (i.e. needle gauge) have been investigated; however there is no investigation on the method of cerebrospinal fluid (CSF) collection. **Objective:** To investigate whether mild CSF aspiration is associated with increased PDPH in selected patients. **Methods:** 336 subjects were eligible to the study. Data on 237 patients from a tertiary neurology hospital who underwent diagnostic LP from February 2010 to December 2012 were analysed. Patient demographics, lumbar puncture method, CSF biochemical characteristics, opening pressures, and a follow-up inquire on PDPH occurrence were collected. CSF was collected either by allowing free flow or by mild aspiration. **Results:** The aspiration arm (n=163) was comprised of 55.8% females with mean age of 52(35–69) years. Sex distribution was not different between the two arms (p=0.191). A significant larger amount of CSF was obtained in the aspiration arm (p=0.011). The incidence of PDPH in the aspiration arm was 16.5% versus 20.2% in the free flow arm, not statistically significant (p=0.489). No relevant associations emerged from the analyses in the subgroup aged <65 years. **Conclusions:** Aspiration of the CSF during LP was not associated with increased rates of PDPH compared to the standard method, particularly when larger amounts of CSF are required and ideal conditions are met. This is the first study looking into this matter, aiming to add safety to the procedure. Further randomized trials are required.

Keywords: cerebrospinal fluid; headache; post-dural puncture headache; spinal puncture.

RESUMO

Introdução: Cefaleia pós-punção dural (CPPD) é uma condição iatrogênica após punção lombar (LP). Incidência é variável; frequentemente associada a mulheres jovens. Características técnicas do procedimento (ex: calibre da agulha) foram investigadas; no entanto, não há investigação sobre o método de coleta do líquido cefalorraquidiano (LCR). **Objetivo:** Avaliar se aspiração leve do LCR está associada ao aumento da CPPD em pacientes selecionados. **Métodos:** 336 indivíduos foram elegíveis para o estudo. Dados de 237 pacientes em um hospital neurológico terciário que foram submetidos à PL diagnóstica de fevereiro de 2010 a dezembro de 2012 foram analisados. Coletamos dados demográficos dos pacientes, método da PL, características bioquímicas do LCR, pressões de abertura e ocorrência da CPPD. Todos as PLs ocorreram em decúbito lateral. O LCR foi coletado permitindo livre fluxo ou aspiração leve. **Resultados:** O grupo aspiração (n=163) apresentava 55,8% de mulheres, idade média de 52(35–69) anos. A distribuição por sexo não foi diferente entre os dois grupos (p=0,191). Uma quantidade maior de LCR foi obtida no grupo aspiração (p=0,011). A incidência de CPPD no grupo de aspiração foi de 16,5% versus 20,2% no fluxo livre, não estatisticamente significativa (p=0,489). Nenhuma associação emergiu das análises no subgrupo com idades <65 anos. **Conclusões:** A aspiração do LCR durante PL não está associada ao aumento da CPPD em comparação com a método padrão, particularmente quando quantidades maiores de LCR são necessárias e condições ideais são satisfeitas. Este é o primeiro estudo a investigar o tópico, visando aumentar a segurança do procedimento. Necessita-se futuros estudos randomizados.

Palavras-chave: líquido cefalorraquidiano; cefaleia; cefaleia pós-punção dural; punção espinal.

¹Instituto de Neurologia de Curitiba (INC), Departamento de Neurologia, Curitiba PR, Brazil.

²Gosford Hospital, Neurology Department, NSW, Australia.

³Neuroscience Research Australia (NeuRA), NSW, Australia.

⁴Centro de Memória de Curitiba (CMC), Curitiba PR, Brazil.

Rodrigo Tomazini MARTINS  <https://orcid.org/0000-0002-6415-0310>; Barbara TOSON  <https://orcid.org/0000-0001-6661-9971>;

Ricardo Krause Martinez de SOUZA  <https://orcid.org/0000-0003-2161-2666>; Pedro Andre KOWACS  <https://orcid.org/0000-0001-7770-7475>

Correspondence: Rodrigo Tomazini Martins; Neurology department, Gosford Hospital; 60 Holden Street, Gosford, NSW, 2260, Australia; E-mail: rodrigo.tomazinimartins@health.nsw.gov.au

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An adult has approximately 150 mL of cerebral spinal fluid (CSF) in the neuroaxis at one time¹ and it is renewed 3 to 4 times a day^{2,3}. CSF is produced continuously at a rate of 0.4 mL/minute in adults, totaling 500 mL per day⁴. Therapeutic removal of CSF through the dura-mater was first performed independently by Heinrich Quincke and Walter Wynter in 1891 to relieve raised intracranial pressure⁵. In horizontal decubitus under normal conditions, CSF pressure measured at the lumbar region ranges from 5 to 15 cm H₂O⁶.

Although lumbar puncture (LP) is a relatively safe procedure, several adverse effects have been reported, including headache and intracranial hemorrhage⁷. It is a major iatrogenic cause of morbidity in patients who underwent anesthesia, epidural blockage, and diagnostic LP^{8,9}. A dural tear yields excessive CSF leakage, leading to intracranial hypotension and reduced CSF volume^{8,10,11}; however, dural repair occurs by fibroblastic proliferation of the surrounding tissue and blood clot formation^{6,12,13}.

August Bier was the first to report the post-dural puncture headache (PDPH) in 1898^{2,9} after injecting 10-15 mg of cocaine in the subarachnoid space of seven patients^{11,14,15}. PDPH diagnosis is based on its clinical presentation and history of previous LP, with evidence of slightly increased CSF protein and lymphocytic pleocytosis in the CSF^{16,17}. In 90% of PDPH patients, headache ensues within 72 hours post LP and is self-limited^{11,11}.

Ever since LP has been routinely performed, PDPH incidence was reported ~66%, ranging from 10-80%^{3,13,15}. The largest cohort of PDPH ever published included 11,000 patients who underwent LP and reported 50% occurrence¹¹. The introduction of atraumatic needles was responsible by a markedly reduction in the incidence of PDPH^{8,18,19}. However, despite the American Academy of Neurology (AAN) recommendations, less than 2% of neurologists routinely use it^{8,12,15,19}. Yet a variable 10-24% PDPH incidence is reported with Quincke needles^{20,21}.

Young adults¹⁷, particularly females, tend to be more affected (3:1)¹³. A four-fold higher incidence around the fourth decade of life is described^{2,18}, while older adults are less susceptible to it^{1,15,22}. PDPH is also infrequent in clinically demented patients²³ and specifically in normal pressure hydrocephalus²⁴. A high incidence is also reported among females with low BMI^{12,19} and higher rates of PDPH are reported post LPs performed at emergency departments²⁵.

While variable amount of CSF is required for diagnostic tests, samples for fungal culture or tap test require volumes in excess of 30 mL^{22,24} which can be time consuming. Duration greater than 6 minutes to collect 2 mL of CSF through a 22G needle allowing free flow was reported²⁶. Although most authors recommend free flow CSF collection, some advocate a mild aspiration by negative pressure can be performed^{15,19,27,28,29}. However, safety and tolerability of this technique were never prospectively reported.

The present study aimed to investigate the incidence of PDPH in patients subjected to CSF aspiration during LP, comparing it to the standard technique, as well as to document its safety and tolerability.

METHODS

Design and participants

This study included neurological patients who underwent diagnostic LP from February 2010 to December 2012 at Neurological Institute of Curitiba (Brazil). Outpatients who attended the emergency department and inpatients that underwent diagnostic LP were recruited for the study. Subjects had a full anamnesis and neurological examination performed by a staff member followed by any modality of neuroimaging (i.e. CT or MRI brain) to exclude contraindications, prior to the LP was recommended and performed. Exclusion criteria consisted of refusal to take part of the study or consent withdrawal, lack of recent (<2 days) neuroimaging result, blood diathesis, or the presence of other medical contraindication - i.e. anticoagulation, lumbar region skin infection or more than two attempts for a successful LP. All included subjects consented to participate. Study protocol was approved by the local regulatory board.

Lumbar puncture

LP was performed according to the standard technique adopted within the institution for diagnostic purposes across a wide spectrum of neurological disorders. Patients were positioned in left lateral decubitus with knees flexed and back arched. Antisepsis of the lumbar region was performed; a sterile drape was placed, followed by subcutaneous infiltration of Xylocaine 1% without vasoconstrictor (5 mL). A Quincke spinal needle 22G (Spinocan[®]) with metallic stylet was introduced at an angle of ~60° with the skin at the midline. Bevel was oriented longitudinally and the needle was progressed to the subarachnoid space at the interspace level of L3-L4. In case of failure, only another attempt at L4-L5 was performed after new infiltration with local anesthetic. It was followed by spinal manometry and CSF collection into sterile jars. Outpatients had the CSF collected by free flow, as much as required for the diagnostic tests proposed. Inpatients had CSF collected by mild aspiration via negative pressure with a glass syringe at a rate 3 mL/minute. Upon collection, a compressive dressing was applied and all subjects were instructed to remain in horizontal decubitus for 60 minutes. All samples were taken immediately to the onsite pathology laboratory for CSF analysis.

Data collection

Demographic data including sex, age, amount of CSF collected, opening pressure, method of collection, and the

encounter where the procedure occurred were obtained from patients' files. CSF biochemical characteristics were collated from onsite pathology laboratory reports and BMI, when available, was obtained from dietician's reports. BMI data was not available for outpatients. Two weeks after the diagnostic LP, subjects were inquired personally or via phone call about the occurrence of PDPH, as defined by The International Classification of Headache Disorders 2nd edition (ICHD-2)³⁰ asking a simple question: "Did you experience headache up to seven days after the diagnostic lumbar puncture, that was triggered a few minutes after assuming upright position and subsided within 30 minutes after reclining?". Dichotomous answers allowed (YES or NO) were recorded.

Statistical analyses

IBM SPSS v24.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Missing values analysis and binary indicator (0=available, 1=missing) of the variables of interest were used to investigate missing data patterns. Categorical variables such as sex, method of CSF collection, and age group were summarized with numbers (n) and percentages (%). The normality distribution of the continuous variables such as age, BMI, opening pressure, volume of CSF collected, CSF red blood cell count, mononuclear cell count, and protein levels was investigated using the Shapiro-Wilk test, concluding that all variables are not normally distributed. Descriptive statistics of non-normally distributed variables were expressed as median (interquartile range - IQR). Differences between groups were tested using chi-square and Mann-Whitney test for categorical and continuous non-parametric variables respectively. Logistic regression was used to investigate the relationship between volume of CSF collected and PDPH.

Outcomes

The primary outcome was to determine the rate of PDPH post CSF aspiration during LP and identify differences in outcomes using individuals and CSF biochemical characteristics. The secondary outcome was to compare the rate of PDPH by free flow *versus* mild aspiration within the institution and to discuss against the relevant literature available.

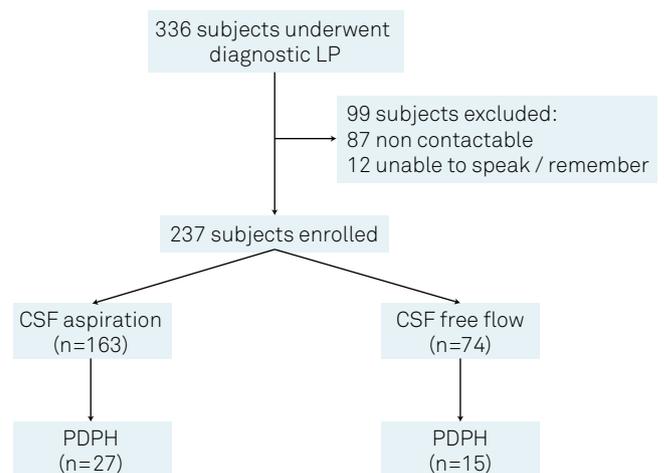
RESULTS

A total of 336 patients were eligible for the study (Figure 1). Missing PDPH data amounted to 99 cases (29.5%), of which 87 were lost follow-up and the remaining were unable to speak (n=7) or recall (n=5). A pattern was identified for the missing BMI data (33.3%). There was a strong association between missing BMI and missing PDPH data (chi-square=40.276; d.f.=1; p<0.001), and missing BMI and method of CSF collection (chi-square=27.937; d.f.=1; p<0.001), with a greater number of participants missing BMI measurements if recruited during an ED presentation (53.9%) *versus*

inpatients (24.4%). Given the study design this is most likely indicative of protocol failure with collecting BMI data during an ED presentation. Information on opening pressure was missing in 19 cases (5.7%) but was not significantly associated with PDPH missing values, as none of the other predictors. For these reasons analysis was limited to the participants with complete information on PDPH (n=237) and BMI was excluded from the analysis.

Demographic of subjects and their CSF laboratorial features according to the method of CSF collection are displayed in Table 1. Group CSF aspiration (n=163) had 91 females (55.8%) and had median age of 52 years, whereas group free CSF flow (n=74) was composed of 48 females (64.8%) and had a median age of 42 years. Gender difference between groups was not significant (p=0.191). Aspiration group presented a significantly larger volume of CSF collected than the free flow group (p=0.011).

Overall 17.7% of the participants experienced PDPH within the 14 days follow-up period. Breakdown of this value according to the method of CSF collection was 16.5% of PDPH for aspiration *versus* 20.2% for free CSF flow. This difference was not statistically significant (p=0.489). Most of the participants belonged to the younger group aged under 65 (n=176 vs n=61). The number of participants with PDPH was much larger in the younger group (n=37; 21%) than in the older group (n=5; 8%). The younger participants were significantly more likely to experience PDPH (RR=2.565; CI 1.05-6.229). Univariate analysis results are provided in Table 2. A logistic regression revealed association between volume and the occurrence of PDPH when the method of CSF collection was included in the model. For each additional 1 mL of CSF collected, the odds of developing PDPH is 6% higher (OR=1.063; CI 1.007-1.121; p=0.027). Because of small number of cells in the CSF, it was not possible to perform a multivariate analysis including age group and



LP: lumbar puncture; CSF: cerebrospinal fluid; PDPH: post-dural puncture headache.

Figure 1. CONSORT flowchart of patients' recruitment, enrolment, interventions and primary outcomes per arm.

method of CSF collection. Instead, a subgroup analysis on participants younger than 65 (n=176) was performed (Table 3). No significant associations emerged when comparing the key parameters in the younger population for the occurrence of PDPH. Finally, there were not statistically significant differences between the methods of CSF collection.

DISCUSSION

Occurrence of PDPH was found to be similar between the two methods of CSF collection tested. To be consistent, the AAN recommendations of introducing the needle with the bevel oriented longitudinally^{1,6,15,18}, reinsertion of the stylet prior to needle withdraw³¹, and avoiding multiple attempts¹⁶ were followed. Needles 25 to 22G are recommended for diagnostic LP. The use of 22G needles were elected for this study, being most suitable for spinal manometry allowing optimal CSF flow^{6,13,26} and widely used. Additionally, larger gauge needles do require less negative pressure to aspirate CSF at the same flow rate, compared to a thinner one. A paramedian

approach was described by some authors to reduce risk of PDPH^{2,11}. However, midline access provides easier identification of anatomical structures and was adopted in the study. That approach has recently not been proved to reduce the risk of PDPH as compared to the latter³². Although bed rest post LP had been described to reduce PDPH severity¹ or delay its onset¹⁸, several studies failed to prove it to be more effective than early ambulation after LP in the prevention of PDPH^{10,33}. Despite the lack of evidence, we opted for keeping all patients resting in bed post LP for 1 hour.

Concordant with Seupaul and colleagues²⁵, we found that PDPH occurred more frequently in those who underwent LP in the emergency department. The incidence reported in this manuscript meets with the commonly reported 30% incidence of PDPH in this setting¹⁶. Nonetheless, in those whom the CSF was aspirated, findings were unexpected. The authors hypothesised the incidence of PDPH would be greater with CSF aspiration, when in fact it proved to be marginally lower. Although this difference was not statistically significant, it could be explained by a thicker dural membrane

Table 1. Participants' characteristics according to the method of CSF collection.

| Method of CSF collection | Aspiration (n=163) | Free flow (n=74) | p-value |
|---|---------------------|---------------------|---------|
| Female, n (%) | 91 (55.8) | 48 (64.9) | 0.191 |
| Age (years), median (IQR) | 52 (35–69) | 42 (30–54) | 0.002* |
| Age under 65 years, n (%) | 113 (69.3) | 63 (85.1) | 0.010* |
| Opening pressure (cmH ₂ O), median (IQR) | 16 (13.5–21.0) | 17 (13.00–19.00) | 0.818 |
| Volume of CSF collected (ml), median (IQR) | 10 (5–15) | 7 (5–10) | 0.011* |
| CSF red blood cells count (x10 ⁶ /L), median (IQR) | 1 (0.3–3.0) | 1 (0.3–4.0) | 0.760 |
| CSF Mononuclear cells count (x10 ⁶ /L), median (IQR) | 0 (0–0) | 0 (0–0) | 0.858 |
| CSF protein level, median (mg/dl) (IQR) | 45.60 (34.20–63.25) | 41.85 (31.75–65.25) | 0.391 |

CSF: cerebrospinal fluid; cmH₂O: centimeters of water; IQR: interquartile range; *indicates statistically significant.

Table 2. Determinants of PDPH: displaying p values for univariate analysis.

| Characteristic | No PDPH (n=195) | PDPH (n=42) | p-value |
|--|---------------------|---------------------|---------|
| Female, n (%) | 111 (56.9) | 28 (66.7) | 0.245 |
| Age (years), median (IQR) | 52.0 (31–66) | 45.5 (35–57) | 0.438 |
| Age under 65 years, n (%) | 139 (71.3) | 37 (88.1) | 0.024 |
| Method of CSF collection | | | 0.489 |
| Free Flow, n (%) | 136 (69.7) | 27 (64.3) | |
| Aspiration, n (%) | 59 (30.3) | 15 (35.7) | |
| CSF Opening pressure (cmH ₂ O), median (IQR) | 16 (13.0–21.0) | 16 (13.5–19.5) | 0.930 |
| Volume of CSF collected (ml), median (IQR) | 10 (5–15) | 7 (5–10) | 0.690 |
| CSF Red blood cell count (x10 ⁶ /L), median (IQR) | 1 (0.3–3.6) | 1 (0.3–2.0) | 0.534 |
| CSF Mononuclear cell count (x10 ⁶ /L), median (IQR) | 0 (0–0) | 0 (0–0) | 0.156 |
| CSF protein level, median (mg/dl) (IQR) | 46.65 (33.60–66.20) | 38.85 (34.30–50.10) | 0.150 |

PDPH: post-dural puncture headache.

in those individuals. Amorim and colleagues have already demonstrated that a thinner dura-mater accounts for 50% higher CSF leakage compared to a thicker one². This phenotype is inherent to individuals and cannot be attributed as a bias of selection. Furthermore, Valença et al.³⁴ demonstrated that CSF leakage is variable within an individual as a result of variable dural thickness. These findings have the potential to explain the opposite direction of our findings.

Several studies report increased incidence of PDPH in younger patients, particularly females^{35,36}. We found similar trends in our study, however sex did not show to play a role. Also, older age seems to be protective, regardless of the method of CSF collection used. Similar to our findings, low incidence of PDPH in the elderly was also observed by Malm and colleagues²².

Unlike other authors who also did not demonstrate any relationship between the amount of CSF collected and PDPH occurrence^{16,37}, our findings revealed a slight increase in the occurrence of PDPH. This was not as marked as Hammond and colleagues conclusions¹², who reported 1.8-fold higher risk of PDPH for each extra 5ml of CSF collected. Additionally, similarly to our findings, recently Monserrate and colleagues³⁸ reported a protective effect of collecting CSF volumes of up to 30 mL, albeit safely and tolerably.

Alike to Kim and colleagues⁷, we found that the opening pressure measured during spinal manometry in the lateral decubitus was not related to PDPH occurrence.

The term “*blood patch*” emerged in 1962¹. It alluded that traumatic LP (i.e. “bloody tap” - presence of >5 red blood cells/mm³ of CSF)¹² was associated with lower incidence of PDPH^{6,13}. This association did not emerge in our sample given the very low red blood cell count in the CSF samples across the two distinct methods of CSF collection.

Finally, the fact that protein levels were not statistically different between the two methods of CSF collection, regardless of the PDPH occurrence or not, suggests that mild aspiration of the CSF may not cause red or white cells lysis. This would be a concern which could invalidate CSF analysis as demonstrated by Chow and Schmidley³⁹ from CSF samples obtained from a traumatic LP left for a prolonged period unrefrigerated.

In spite of being the first study ever to investigate the use of this technique for clinical diagnostic LP, when sometimes a large amount of CSF is required, this study has several limitations. Firstly, an observational study design is not ideal. Despite a potential selection bias, an institutional regulation only allowed the use of glass syringes with inpatients. Secondly, there was a substantial amount of missing data, particularly BMI in patients that were not admitted after the procedure, which may have contributed to a less precise analysis. Also, there may be bias of selection of techniques according to the location where patients were first seen by the treating physician and had the LP done. However, these limitations are outweighed by the lack of increased rates of PDPH when comparing both techniques. In contrast, the strengths include the novel investigation and the relatively large cohort analyzed with the technique. Nonetheless, the study may pave the way for future investigations with more rigid protocols targeting for specific age groups, headache onset, intensity, and duration or other features commonly associated with this condition.

Therefore, this study demonstrates that the aspiration of the CSF during LP is not associated with increased rates of PDPH compared to the standard technique (free flow). This adds to safety for performing a mild CSF aspiration, particularly when larger amounts of CSF are required in older patients. This is a valuable technique that could be employed at a busy neurology department, when the ideal conditions are met, without increasing the risk of PDPH.

Table 3. Results of subgroup analysis (under 65 years).

| Characteristic | No PDPH (n = 139, 79%) | PDPH (n = 37, 21%) | p value |
|---|------------------------|---------------------|---------|
| Female, n (%) | 82 (59.0) | 27 (73.0) | 0.120 |
| Age (years), median (IQR) | 41 (27–53) | 43 (35–52) | 0.257 |
| Method of CSF collection | | | 0.631 |
| Aspiration, n (%) | 88 (63.3) | 25 (67.6) | |
| Free Flow, n (%) | 51 (36.7) | 12 (32.4) | |
| CSF opening pressure (cmH ₂ O), median (IQR) | 17 (14–21) | 16 (13–20) | 0.666 |
| Volume of CSF collected (ml), median (IQR) | 7 (5–10) | 6 (5–10) | 0.458 |
| CSF red cell count (n), median (IQR) | 1.0 (0.3–5.0) | 1.0 (0.3–2.0) | 0.500 |
| CSF mononuclear cells count (x10 ⁶ /L), median (IQR) | 0 (0–0) | 0 (0–0) | 0.124 |
| CSF protein level (mg/dl), median (IQR) | 47.30 (30.80–68.80) | 37.70 (34.30–47.80) | 0.282 |

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