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Gender and Post–Dural Puncture Headache

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Gender is believed to be an independent risk factor for the development of post–dural puncture headache, but there are some of the inconsistencies in the available data. This systematic review examined a total of 18 trials (2,163 males, 1,917 females). The odds of developing a post–dural puncture headache were significantly lower for male than nonpregnant female subjects (odds ratio = 0.55; 95% confidence interval, 0.44–0.67). Although the authors found that nonpregnant female subjects seem to have a higher incidence of post–dural puncture headache than males, the etiology behind these findings is not clear from the current meta-analysis.

GENDER is believed to be an independent risk factor for the development of post–dural puncture headache (PDPH). Females are generally believed to have a higher incidence of PDPH; however, previous data[1] may not have adjusted for parturients (22% incidence of PDPH[1]) who may have received relatively more lumbar punctures than similarly aged males and, as a result, may have skewed previous data examining the overall incidence of PDPH (*i.e.*, 7% for males *vs.* 14% for females overall[1]). Some data in the anesthesiology literature suggest that there may be no significant difference in the incidence of PDPH between males and females.[2–4] For example, a multivariate analysis of 1,021 spinal anesthetics noted that gender was not a significant predictor of PDPH ($P = 0.12$). However, other randomized data indicate that females may have a higher incidence of PDPH compared with males (7.4% for females *vs.* 3.4% for males).[5]

There may be several reasons why females may have a higher incidence of PDPH. It is well recognized that females have a higher incidence of certain types of headaches, such as tension type and migraine.[6,7] In addition, there may be differences in the processing of nociceptive information such that females may exhibit greater sensitivity to experimentally induced pain and demonstrate greater temporal summation of mechanically evoked pain.[8–10] Finally, some data also suggest that sex hormones may influence the incidence of certain types of headaches,[11,12] but other data suggests that hormonal levels may not influence the incidence of PDPH.[13] Because of some of the inconsistencies in the available data, we performed a meta-analysis of randomized trials to determine the extent of gender (excluding parturients) as a risk factor for the development of PDPH.

Materials and Methods

The National Library of Medicine's PubMed database was searched for the time period 1966 to August 31, 2004. PubMed was searched for all articles containing text words *postdural puncture headache* (13,866 articles), *spinal headache* (13,823 articles), and *headache* (33,467 articles), which yielded a total of 33,467 articles. A second search was performed using the text words *epidural anesthesia* (10,255 articles), *spinal anesthesia* (7,639 articles), *lumbar puncture* (5,097 articles), *myelogram* (7,487 articles), and *spinal* (193,389 articles), which yielded a total of 205,145 articles. These two searches were combined using the Boolean term *AND* (3,025 articles). This search was limited to the English language (2,213 articles) and then to human subjects, which resulted in 306 abstracts. The full article of each abstract was then reviewed by one of the authors for inclusion into the meta-analysis. No minimum sample sizes were invoked for inclusion of studies in the analysis. Any disputes were resolved by agreement of at least two reviewers.

For the purposes of this meta-analysis, PDPH was defined a headache occurring after a single lumbar puncture that was postural in nature. To be included in this meta-analysis, the postural component of PDPH needed to be clearly indicated in the article. Other inclusion criteria included trials that were randomized, that evaluated only adult patients, and where the incidence of PDPH studied and the data were available for both genders. Exclusion criteria included articles where definition of PDPH was unclear (*i.e.*, did not indicate a postural component of the headache), only one gender was studied (*e.g.*, parturients), the separate incidence of PDPH for male and nonpregnant female subjects was not available, or randomization of subjects was not performed. We excluded any studies that examined parturients because the physiologic changes in pregnancy may potentially influence how pain (including headache) is perceived, and the main focus of our meta-analysis was on a comparison of PDPH between nonpregnant females and males. Our meta-analysis also excluded articles investigating the incidence of PDPH after a continuous spinal catheter.

Data (*e.g.*, study characteristics, type and size of lumbar puncture needle, number and mean age of males and

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Table 1. Overview of Studies

Study, Year	Type of Surgery	n Total (M/F)	Needle Size/Type	PDPH Male	PDPH Female
Tourtellotte *et al.*,[31] 1972	LP	100 (61/39)	22 + 26G Q	9/61 (15%)	15/39 (38%)
Hilton-Jones *et al.*,[20] 1982	LP	76 (37/39)	20G Q	11/37 (30%)	18/39 (46%)
Vilming *et al.*,[32] 1988	LP	300 (150/150)	22G Q	60/150 (40%)	89/150 (59%)
Rasmussen *et al.*,[26] 1989	MIX	376 (235/141)	20 + 25G Q	35/235 (15%)	21/141 (15%)
Sengupta *et al.*,[28] 1989	GU	48 (36/12)	25G Q	8/36 (22%)	5/12 (42%)
Dahl *et al.*,[16] 1990	ORTHO	50 (38/12)	29G Q	1/38 (3%)	0/12 (0%)
Kang *et al.*,[5] 1992	MIX	658 (320/338)	26 + 27G Q	11/320 (3%)	25/338 (7%)
Pippa *et al.*,[24] 1995	ORTHO	160 (83/77)	21 + 25G Q	4/83 (5%)	9/77 (12%)
Corbey *et al.*,[15] 1997	MIX	183 (123/60)	27G W, 27G Q	3/123 (2%)	2/60 (3%)
Strupp and Brandt,[29] 1997	LP	600 (240/360)	21G S	24/240 (10%)	46/360 (13%)
Despond *et al.*,[18] 1998	ORTHO	194 (145/49)	27G W, 22G Q	8/145 (6%)	10/49 (20%)
Puolakka *et al.*,[25] 1998	ORTHO	50 (26/24)	26 + 27G W	0/26 (0%)	1/24 (4%)
De Andres *et al.*,[17] 1999	ORHTO	158 (123/35)	26 + 27G W	2/123 (2%)	4/35 (11%)
Strupp *et al.*,[30] 2001	LP	230 (84/146)	22G W, 22G Q	15/84 (18%)	28/146 (19%)
Linker *et al.*,[22] 2002	LP	100 (43/57)	25G W	1/43 (2%)	3/57 (5%)
Murata *et al.*,[23] 2003	LP	198 (123/75)	21G Q	9/123 (7%)	14/75 (19%)
Esmaoglu *et al.*,[19] 2004	ORTHO	70 (47/23)	25G Q	11/47 (23%)	4/23 (17%)
Santanen *et al.*,[27] 2004	MIX	529 (249/280)	27G W, 27G Q	1/249 (0.4%)	7/280 (3%)

ABD = abdominal surgery; G = gauge; GU = urologic surgery; LP = lumbar puncture for diagnostic purposes (*e.g.*, myelogram); MIX = mixed surgical procedures; ORTHO = orthopedic surgery; PDPH = post–dural puncture headache; Q = Quincke; S = Sprotte; W = Whitacre.

nonpregnant female subjects, incidence of PDPH) were collected from each article, and results were recorded. Data were extrapolated from figures or tables as needed; however, an attempt was made to contact the original authors before extrapolation. All reported data were included as unique observations and subgrouped as described below. PDPH data were weighted by sample size. The overall incidence of PDPH (weighted for patient observations) after lumbar puncture between male and nonpregnant female subjects were compared. The data for incidence of PDPH was subdivided by needle type (*e.g.*, cutting *vs.* pencil point), needle size, and age.

The level of significance for all tests was set at an α level of 0.05. Demographic data were compared with chi-square (needle size and shape) and *t* tests (age). A fixed effects model was used. All statistical analyses (*i.e.*, determination of the pooled estimate, test for heterogeneity) were performed with RevMan 4.2.7 (The Cochrane Collaboration, 2004) and SPSS 10.0.7 (SPSS Inc., Chicago, IL). After the data compilation was complete, we performed further analyses to assess the validity of our conclusions. We performed an analysis of the file drawer problem (*i.e.*, how many unpublished studies or subjects showing no difference between treatment regimens would be needed to be "discovered" in someone's file drawer to invalidate our results) as described by Rosenthal.[14]

Results

Our search resulted in 306 abstracts of which a total of 18 articles[5,15–32] met all inclusion criteria. There were 2,163 male subjects and 1,917 nonpregnant female subjects in the 18 randomized trials used for the meta-analysis. A total of 288 articles were rejected for the following reasons: 113 did not include an adequate definition of PDPH (*i.e.*, did not indicate a postural component of the headache), 68 assessed only one gender, 34 did not provide breakdown data for incidence of PDPH for male and female subjects, 35 were not randomized, and 38 were pediatric studies.

Table 1 provides a detailed overview of studies included in the analysis. Table 2 shows the characteristics of the studies used for the meta-analysis. The majority of studies were from Europe (13 trials) and only performed their study in one center (16 trials). Table 3 shows the demographic and study data arranged by gender. There were more male (2,163 or 53%) than nonpregnant female (1,917 or 47%) subjects. Nonpregnant female subjects overall were significantly older (42.5 ± 7.0 *vs.* 38.8 ± 9.8 yr, mean ± SD; $P < 0.001$) than male subjects. There were no significant differences in the percentages of pencil-point spinal needles or size of spinal needles between the two groups. Table 4 shows the adjusted incidence of PDPH stratified by needle size and shape. We were not able to provide a meaningful weighted incidence stratified by age because of the paucity of data (*i.e.*, not all trials provided breakdown of age by gender).

Figure 1 shows the pooled estimate of all included studies. The variation in results across studies (*i.e.*, heterogeneity) was not statistically significant ($I^2 = 22.0$, $P = 0.19$). The odds ratio of a male subject developing a PDPH *versus* a nonpregnant female subject was 0.55 (95% confidence interval, 0.44–0.67), *i.e.*, male subjects have approximately one half of the odds of developing PDPH compared with nonpregnant female subjects (or the odds of developing a PDPH are approximately 2 times greater in female than in male subjects). A file drawer analysis of our data revealed that 1,731 subjects showing no difference in the incidence of PDPH be-

Table 2. Study Characteristics

Number of subjects (total = 4,080)	
Male	2,163
Female	1,917
Center location (number of trials)	
Europe	13
North America	3
Asia	1
Canada	1
Number of study centers	
2–5 centers	1
1 center	16
Not reported	1
Needle type (number of trials/number of data points)	
Cutting	13/32
Pencil point	7/18
Both	1/2
Needle size (number of trials/number of data points)	
20 gauge	2/4
21 gauge	2/4
22 gauge	3/8
25 gauge	4/8
26 gauge	4/8
27 gauge	6/16
≥ 28 gauge	1/2
Unadjusted incidence of post–dural puncture headache	
Male	213/2,163 = 9.8%
Female	301/1,917 = 15.7%

tween male and nonpregnant female subjects would be needed to nullify our results.

Discussion

The extent of gender as an independent risk factor for the development of PDPH is not clear.[33] We performed a meta-analysis of available randomized trials to determine the effect of gender on the incidence of PDPH and found that nonpregnant female subjects had significantly higher odds of developing PDPH than male subjects. This finding occurred despite the fact that nonpregnant female subjects overall were significantly older, which would theoretically favor a lower incidence of PDPH in female subjects.[3,26] There were no significant differences between the two groups in other factors (*i.e.*, type of spinal needle or needle size) that might have influenced the incidence of PDPH.[34]

Table 3. Demographic Data

	Male	Female	*P* Value
Total subjects, n (%)	2,163 (53%)	1,917 (47%)	0.55
Age, mean ± SD, yr	38.8 ± 9.8	42.5 ± 7.0	< 0.001
Needle type, n (%)			0.26
Cutting	1,360 (62.9%)	1,139 (59.4%)	
Pencil point	658 (30.4%)	729 (38%)	
Unspecified/other	145 (6.7%)	49 (2.6%)	
Needle size, n (%)			0.92
20 gauge	160 (7.4%)	107 (5.6%)	
21 gauge	363 (16.8%)	435 (22.7%)	
22 gauge	262 (12.1%)	318 (16.6%)	
25 gauge	238 (11.0%)	165 (8.6%)	
26 gauge	263 (12.2%)	213 (11.1%)	
27 gauge	756 (35.0%)	590 (30.8%)	
≥ 28 gauge	38 (1.8%)	12 (0.6%)	
Unspecified/other	83 (3.8%)	77 (4.0%)	

n = actual number of subjects.

Although it is not apparent why nonpregnant females would have a higher incidence of PDPH, there may be several physiologic, anatomical, or psychosocial possibilities to explain the higher reported incidence of PDPH in nonpregnant females. Female subjects seem to process nociceptive information differently than male subjects. Although this topic is complex, it seems that female subjects generally exhibit greater sensitivity to experimental noxious stimuli than males.[10,35,36] Females also have higher temporal summation of mechanically evoked pain, indicating that females may demonstrate a greater degree of central sensitization compared with males.[9] Gender differences in patterns of cerebral activation in response to noxious stimuli are also noted, with females having greater activation of the contralateral prefrontal cortex, an activation pattern associated with increased pain perception.[8,37] In addition to gender differences in nociceptive thresholds and processing, there may be psychosocial factors that may contribute to some of the differences seen in experimentally induced pain.[38] Socially learned, gender role expectations of pain may influence the incidence of reported pain because male subjects are less likely to disclose the presence of pain than female subjects, and these psychosocial variables may contribute to a significant portion of the differences seen.[38,39] Postoperatively, females report a higher incidence of headache and pain despite possibly having a greater analgesic response to opioids than men.[40–42] Therefore, both biologic and psychosocial factors may contribute to the differences in pain perception, which may in part explain the increased incidence of reported PDPH in female subjects in our study.

There are other reasons why females might hypothetically report a higher incidence of PDPH. Vasodilation of the cerebral vessels normally occurs in patients with PDPH as a homeostatic mechanism to compensate for cerebrospinal fluid loss and may theoretically contribute to the severity of PDPH.[43–46] Gender differences in the cerebral vasodilatory response are present with premenopausal females exhibiting significantly greater vasodilatory response to acetazolamide than males or postmenopausal females.[47,48] In addition, the incidence of PDPH seems to increase in females relative to male subjects after onset of puberty.[49] Estrogen has been shown to mediate cerebral artery tone and may dilate cerebral pial vessels.[50,51] Finally, younger (aged 30–40 yr), presumably premenopausal women have a signifi-

Table 4. Adjusted Incidence of PDPH for Different Needle Factors

	Unadjusted Incidence of PDPH		Weighted (Adjusted)	
Needle Factor	Male, n/N (%)	Female, n/N (%)	OR (95% CI)	*P* Value
Needle type				
Cutting	174/1,360 (12.8%)	225/1,139 (19.8%)	0.60 (0.48–0.74)	<0.001
Pencil point	33/658 (5%)	64/729 (8.8%)	0.55 (0.36–0.85)	0.006
Needle size				
20–22 gauge	151/785 (19.2%)	218/860 (25.3%)	0.70 (0.56–0.89)	0.003
23–25 gauge	29/238 (12.2%)	22/165 (13.3%)	0.90 (0.50–1.63)	0.76
≥ 26 gauge	31/1,057 (2.9%)	50/815 (6.1%)	0.46 (0.30–0.73)	0.001

Available data used to determine the independent weighted odds ratios (OR) for each needle factor. Data (*i.e.*, needle type or needle size) that were not specified (see table 2) were not incorporated into the analysis.

CI = confidence interval; n = actual number of post–dural puncture headaches; N = actual number of subjects; PDPH = post–dural puncture headache.

cantly higher cerebrovascular reactivity compared with older women (aged 50–60 yr) and men.[52]

There are several limitations to our study. We were unable to obtain all of the possible data for our meta-analysis because it is possible that not all relevant articles were obtained from our current literature strategy, some of the authors did not respond to our requests, and we were unable to extract the relevant data (*i.e.*, incidence of PDPH for male *vs.* nonpregnant female) for some studies; however, the file drawer analysis suggests that a relatively large number of subjects (approximately 1,700) showing no difference in the incidence of PDPH between male and nonpregnant female subjects would be needed to nullify our results. Although gender cannot be randomized, we limited our meta-analysis to randomized controlled trials because data from observational (nonrandomized) trials may not be of equivalent quality (*e.g.*, less stringent or incomplete data collection than randomized trials, lack of blinding, presence of possible bias or confounding), and combining randomized and nonrandomized data into a single pooled estimate (which is extremely controversial) may distort the results through the introduction of bias and confounding. The trials obtained from our literature search that did not meet our inclusion criteria for further statistical analysis contained 1,908 males, 1,914 nonpregnant females, and 9,566 parturients. The overall incidences of PDPH for this and previous[1] observational data are 6.67% (398 in 5,971) for males and 8.58% (527 in 6,140) for nonpregnant females (unadjusted relative risk of male/female = 0.78; $P < 0.0001$). Although this does corroborate our data (*i.e.*, lower risk for PDPH in males), it is possible

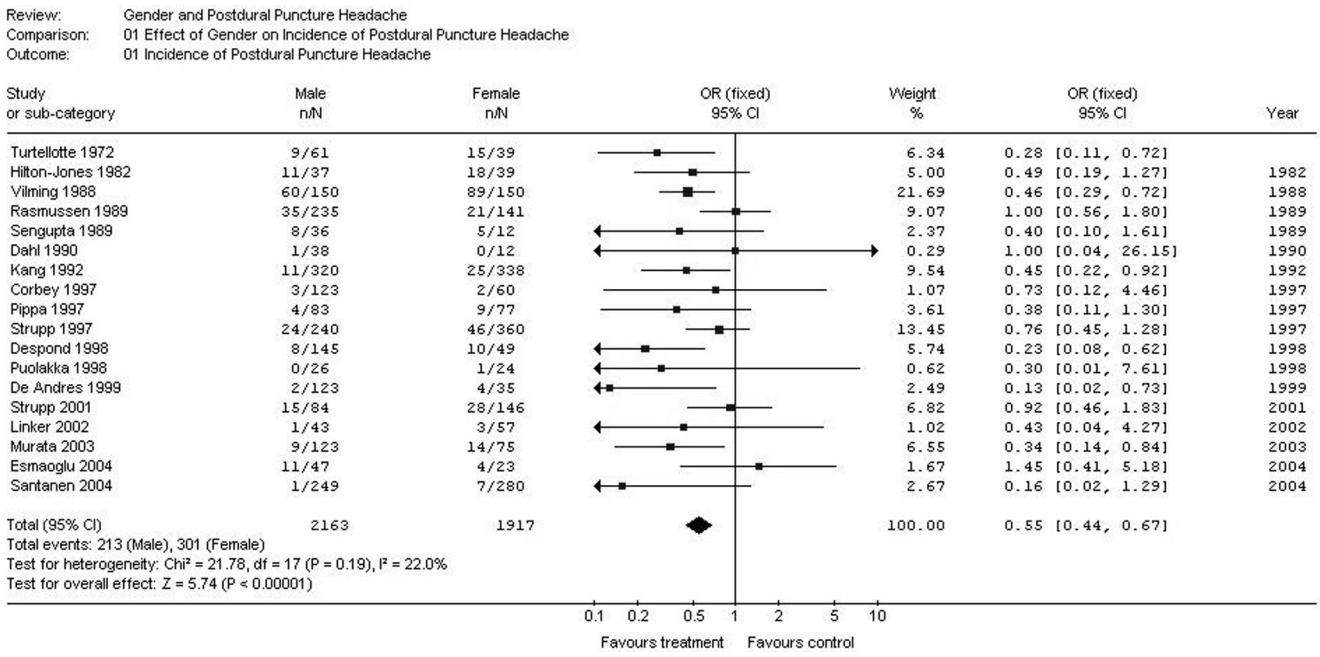

Fig. 1. This figure shows the weighted (pooled) estimate for the incidence of post–dural puncture headache. n represents the actual number of post–dural puncture headaches, and N represents the actual number of male of female subjects. The entire diamond (pooled estimate) lies to the left of the odds ratio (OR) = 1 (which represents no difference), suggesting that male gender is associated with a significant lower odds (odds ratio = 0.55; confidence interval [CI], 0.44–0.67) of post–dural puncture headache than that for females.

that additional analyses and adjustment of observational data may result in different findings than our own. In addition, there may be other observational data not identified by our literature search, which may also provide different results from our data.

Our results may not be generalizable to other populations (which were part of our exclusion criteria) such as parturients or pediatric subjects. Because we excluded studies examining parturients from meta-analysis, we are unable to determine whether parturients may also have a higher relative risk for PDPH *versus* males. We also did not weight by the quality scoring of the randomized controlled trials used or assess the articles in a blinded fashion because the effects of these interventions on the results of meta-analysis are uncertain.[53–56] There are also limitations of the meta-analytic technique *per se*. Discrepancies between meta-analyses and subsequently performed large, randomized controlled trials have been reported, although the reasons for this are controversial.[57–59] There also may be is may be the presence of publication bias because studies that have positive findings are published more frequently in English-language (rather than non–English-language) journals[60,61]; however, the effect of excluding non-English trials on the results of a meta-analysis is uncertain, and the inclusion of these trials may actually result in a more conservative estimate of the treatment effect in some cases.[62]

In summary, our systematic review indicates that female (nonpregnant) gender may be a risk factor for the development of PDPH. Nonpregnant females have approximately twice the odds of developing a PDPH compared with males. Our analysis does not allow us to determine the rationale behind these findings, although several mechanisms may contribute to females having a higher incidence of PDPH. The development of PDPH is a potentially debilitating complication of neuraxial anesthesia, and these techniques should not be withheld from female patients because there are many other potential benefits[63–66] of neuraxial anesthesia and analgesia; however, clinicians consider this higher incidence of PDPH as they weigh the potential risks and benefits of the procedure in females. Nevertheless, clinicians performing lumbar punctures/spinal anesthetics generally should consider implementing available techniques (*e.g.*, use of pencil-point rather than cutting needles, use of smaller-gauge needles, insertion of a beveled needle in a "parallel" rather than "perpendicular" orientation with respect to the dural fibers) to decrease the incidence of PDPH in both genders.

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