Risk of intracranial hypertension with intrauterine levonorgestrel

Ther Adv Drug Saf
2015, Vol. 6(3) 110–113
DOI: 10.1177/2042098615588084

Mahyar Etminan, Hao Luo and Paul Gustafson

Abstract

Objectives: The objective of this study was to quantify the risk of intracranial hypertension (ICH) with the intrauterine levonorgestrel (IUL) device Mirena®.

Methods: We used the United States Food and Drug Administration's Adverse Events Reporting System (FAERS) database to quantify a reporting odds ratio (ROR) for ICH and Mirena®. We also conducted a retrospective cohort study using the IMS LifeLink® database, comparing the risk of two oral contraceptives ethinyl estradiol (EE) with Mirena®. A Bayesian sensitivity analysis was performed to account for the effect of body mass index (BMI).

Results: The reported odds ratios (ORs) for ICH and papilledema with Mirena® were 1.78 (95% confidence interval [CI] 1.41–2.25) and 1.50 (95% CI 1.10–2.05), respectively. In the cohort study, the OR for ICH and EE-norgestimate and EE-norethindrone compared with Mirena® were 1.29 (95% CI 0.83–2.00) and 0.31 (95% CI 0.04–2.29), respectively. The presence of a strong confounder BMI did not affect the estimated OR (OR = 1.31, 95% CI 0.73–2.41 for EE-norgestimate; OR = 0.18, 95% CI 0.01–1.27 for EE-norethindrone).

Conclusion: We found a higher than expected number of reports of ICH with Mirena® in the FAERS database. We also found a similar risk of ICH with Mirena® compared with the oral contraceptive EE-norgestimate. The higher risk of ICH with EE-norethindrone, another oral contraceptive should be further investigated.

Keywords: cohort study, drug safety, intracranial hypertension, intrauterine levonorgestrel

Introduction

Contraceptive medications are one of the most commonly prescribed classes of medications used by young women. While the majority of women use oral contraceptives as the main method of contraception, a considerable proportion opt to use other forms of contraceptive delivery including intrauterine delivery of contraceptive medications. Levonorgestrel is a second-generation progestin that is available both as oral and intrauterine formulations. The intrauterine form of levonorgestrel (IUL) is marketed as Mirena® in North America. IULs may be more convenient for some women as they are implanted in the uterus once. Although the systemic absorption of IULs is thought to be lower than oral formulations, some studies have shown similar rates of adverse events to oral levonorgestrel formulations resulting in discontinuation of up to 50% within the first 6 months of use [Daud and Ewies, 2008]. One serious adverse event that has been associated with progestins [Chan, 2006; FDA, 2014] and specifically Mirena is intracranial hypertension (ICH), a serious medical condition that leads to an increased pressure in the brain and the central nervous system. ICH may be associated with high morbidity including papilledema or swelling of the optic disc which can lead to blindness. There have been several cases [FDA, 2014; Martinez *et al.* 2010] of ICH reported with IUL including one report of a 45-year-old nonobese women in Argentina who developed ICH after 4 years of using IUL [Martinez *et al.* 2010]. Moreover, in light of evidence of ICH with intramuscular and subdermal formulations of levonorgestrel and high variability in systemic absorption of levonorgestrel from IULs [Ewies, 2009], the possible risk of ICS with IULs must be further investigated. Currently, no epidemiologic study has examined the possible association between

Correspondence to:
Mahyar Etminan PharmD, MSc
Therapeutic Evaluation Unit, Child and Family Research Institute of British Columbia, Faculty of Medicine, University of British Columbia, A4-198 WS 2, 709-650 West 28th Avenue, Vancouver, BC, Canada
metminan@popi.ubc.ca, metminan@shaw.ca

Hao Luo, Msc
Paul Gustafson, PhD
Department of Statistics, University of British Columbia, Vancouver, Canada

the risk of ICH with IUL. Given that approximately two million women worldwide use IULs [dailymed, 2014] we sought to quantify the potential risk of ICH with IUL using two epidemiologic approaches.

Methods

We used two different methodologies to answer the study objectives. First, we used the United States Food and Drug Administration's Adverse Events Reporting System (FAERS) database to quantify a reporting odds ratio (ROR) which quantifies the odds of reported cases of ICH amongst Mirena® an IUL used in the United States. The FAERS database captures approximately 5 million reported adverse events [FDA, 2014]. For this analysis we included the following terms: benign intracranial hypertension, idiopathic intracranial hypertension, cerebral edema, intracranial hypertension, papilledema and papilledema, with the date range of 1 January 2004 to 30 September 2013. We specify prior distributions according to the estimates in the medical literature for the prevalence of ICH in the population (10–20/100,000) [Medscape, 2014] and the odds ratio (OR) of ICH with Mirena (1.5–2.5). These prior distributions were then combined with ICH events in the FAERS data using a Bayesian framework to estimate a new ROR which incorporates both data from existing knowledge and real data to estimate an ROR for reported ICH events with Mirena®.

We supplemented the first analysis with a retrospective cohort study that compared the risk of intracranial hypertension between IUL and two other combination oral contraceptives, ethinyl estradiol (EE) and norethindrone and EE-norgestimate. We used a large health claims database, IMS LifeLink® (IMS, USA) which contains over 102 healthcare plans in the United States (IMS, 2014). The database captures health utilization information from all geographic locations in the United States capturing information on approximately 80 million subjects. Specifically, the database captures all hospitalizations, physician visits, procedures and prescription drugs up to 2012. From LifeLink® we had access to aggregate data on women aged 15–45 who were newly prescribed one of the three mutually exclusive contraceptives from 2009–2013: (1) an IUL; (2) an oral formulation of EE-norethindrone; and (3) an oral formulation of EE-norgestimate. We obtained information on intracranial hypertension for the three drug groups by identifying the following conditions: obstructive hydrocephalus idiopathic normal pressure hydrocephalus, benign intracranial hypertension, cerebral edema and papilledema. We did not have information on other medical conditions. We computed an OR between EE-norethindrone and Mirena® as well as EE-norgestimate and Mirena®. One of the potential confounding variables in this study is body mass index (BMI) as it is associated with both ICH and use of IUL [Rowe and Sarkies, 1999]. For example, clinicians may be more likely to prescribe IUL to women with higher BMI due to its slower systemic absorption and potentially lower propensity to cause weight gain. BMI has also been identified as a risk factor for ICHR. Since we did not have information on BMI in our dataset, we used a Bayesian sensitivity analysis (BSA) proposed by McCandless and colleagues [McCandless *et al.* 2007] to incorporate different magnitudes of the effect of BMI on the crude OR for ICH. More specifically, we dichotomized BMI (high *versus* low) to match the scenario presented in McCandless and colleagues. BSA uses a Bayesian framework that generates a distribution for the prespecified ranges of the OR (both for the associations between BMI and IUL and between BMI and ICH). We then incorporated these prior distributions with the crude ORs to obtain a posterior distribution for the OR of Mirena® and ICH that takes into account the effect of different levels of BMI. We assumed two possible ranges for the magnitude of the ORs (OR for BMI and Mirena® = 0.3–3.0; OR for BMI and ICH = 0.16–6.0).

Results

The crude ROR for ICH, papilledema and their combinations did not differ from the Bayesian estimate of OR (Table 1) in the first analysis. The crude and BSA-driven ROR for ICH was 1.78 (95 % CI 1.41–2.25) and 1.85 (95 % CI 1.56–2.18), respectively. In the cohort study, there were 21 new cases of ICH amongst 16,163 new users of IUL. There were also 318 cases of ICH with 190,059 users of EE-norgestimate and one case of ICH with 2501 users of EE-norethindrone. There was no statistically significant difference between the risk of ICH for EE-norgestimate compared with Mirena® users. A trend toward a lower risk of ICH was observed between EE-norethindrone use compared with users of Mirena® although due to a small number of events this difference didn't reach statistical significance.

Table 1. Crude and Bayesian sensitivity analysis adjusted reporting odds ratios for the reported events of intracranial hypertension related events from the FAERS database.

Drug	Crude ROR (95% CI)	Bayesian ROR (95% CI)
ICH	1.78 (1.41–2.25)	1.85 (1.56–2.18)
Papilledema	1.50 (1.10–2.05)	1.74 (1.44–2.11)
Combined outcomes	1.56 (1.28–1.91)	1.70 (1.45–1.98)

CI, confidence interval; ICH, intracranial hypertension; ROR, reporting odds ratio.

Table 2. Crude OR and 95% confidence intervals and Bayesian sensitivity analysis adjusted OR for the presence of weak and strong confounding for the comparison of EE-norgestimate and EE-norethindrone compared to Mirena®.

Drug	Crude OR	Weak confounding	Strong confounding
EE-norgestimate	1.29 (0.83–2.00)	1.31 (0.82–2.18)	1.31 (0.73–2.41)
EE-norethindrone	0.31 (0.04–2.29)	0.18 (0.01–1.26)	0.18 (0.01–1.27)

EE, ethinyl estradiol; OR, odds ratio.

Discussion

Our study is the first large epidemiologic study that that has examined the risk of ICH with Mirena®. The results of our study demonstrate and increased reporting of ICH events with Mirena® from the FAERS database. The results from the cohort study suggest that the risk of EE-norgestimate, an oral formulation, is comparable with that with IUL. We found that compared with IUL, EE-norethindrone is protective for ICH although the small number of events and wide confidence intervals make interpretation of this observation challenging.

Oral and intramuscular contraceptives including progestins have been linked to ICHR [Chan, 2006; FDA, 2014]. Moreover, Norplant®, a contraceptive implant that released levonorgestrel slowly from the upper arm that was believed to have a lower systemic absorption, has also been linked to ICH [Alder *et al.* 1995]. Most reports of ICH secondary to progestins have been with levonorgestrel [Alder *et al.* 1995; Martinez *et al.* 2010] and medroxyprogesterone [Chan, 2006]. There has been one report of ICH with a norethisterone (Sheehan, 1982), an older progestin used previously along with mestranol for hormone replacement therapy. More research is needed to examine the risk of ICH with different formulations of progestins.

IULs such as Mirena® are a unique method of delivering levonorgestrel locally to the endometrium. Although it is not considered a common contraceptive method amongst the wide array of other available drugs or devices, still approximately two million women worldwide are using Mirena®. This number is expected to increase at least in the United States in light of the recent recommendations from the academy of pediatrics on the increase use of IUD as the main method of contraception in adolescents [Committee Adolescence, 2014]. The drug is also marketed as having a lower systemic absorption due to its mode of drug delivery. However, levonorgestrel has shown to bind heavily to sex hormone binding protein system (SHBG) which may differ in concentration in women depending on BMI or ethnicity [Jia *et al.* 1992; Ratsula *et al.* 1989; Nilsson *et al.* 1982]. Thus, the systemic concentration of IUL in women may vary. In fact, studies have shown that after continuous use of IUL, the serum concentration of IUL is variable [Ewies, 2009] and may be comparable with those for the oral levonorgestrel formulations [Ewies A, 2009] providing a pharmacologically plausible explanation for ICH events with IULs.

'Our study is subject to limitations. For the first analysis we used the FAERS database which captures only reported adverse events. Further, we only had aggregate data for our epidemiologic analysis and did not have information for other covariates. However, given that ICH is a rare disease, it is unlikely that adjusting for variables that are only

risk factors and not confounders may have changed the results of our study [Schisterman *et al.* 2009]. We did not have information on all risk factors for ICH. However, we do not believe that given the rarity of ICH, information on other risk factors would have changed the results of this study. The BSA method used to estimate the effect of BMI on Mirena® assumes a logistic regression model (based on a binomial distribution). The true relationship between BMI and Mirena® may however follow other types of models. In summary, we found a similar risk for ICH between Mirena® and an oral contraceptive, EE-norethindrone combination. The higher risk of ICH for Mirena® compared with EE-norgestimate combination should be examined in future studies. The recent recommendations from the American Academy of Pediatrics stressing on the use of IUL by young girls as the main method of contraception underscores the importance of the results of this study. In light of these recommendations and the possible increase in the use of IULs, the risk of ICH with Mirena® must be clearly conveyed to young women who are planning to use them. However, the small risk of ICH may outweigh the risk of unintended pregnancies.

Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

Alder, J., Fraunfelder, F. and Edwards, R. (1995) Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 332: 1720–1721.

Chan, J. (2006) Idiopathic intracranial hypertension associated with depot medroxyprogesterone. *Eye* 20: 1396–1397.

Committee on Adolescence (2014) Contraception for adolescence. *Pediatrics* 134: E1244–E1256.

Daud, S. and Ewies, A. (2008) Levonorgestrel-releasing intrauterine system: why do some women dislike it? *Gynecol Endocrinol* 24: 686–690.

dailymed (2014) MIRENA – levonorgestrel intrauterine device. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=12313 (accessed 2 October 2014).

Ewies, A. (2009) Levonorgestrel-releasing intrauterine system - the discontinuing story. *Gynecol Endocrinol* 25: 668–673.

Medscape (2014) Idiopathic intracranial hypertension. http://emedicine.medscape.com/article/1214410-overview#a0156 (accessed 2 October 2014).

FDA (2014) FDA Adverse Event Reporting System (FAERS). http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm (accessed 2 October 2014).

IMS (2014) IMS LifeLink™ Information Assets Electronic Medical Records. http://www.imshealth.com/deployedfiles/ims/Global/Content/Solutions/Healthcare%20Analytics%20and%20Services/Healthcare%20Outcomes/IMSLifelink-EMR.pdf (accessed 13 October 2014).

Jia, M., Zhou, L., Ren, S., Dong, L. and Xiao, B. (1992) Serum SHBG levels during normal isoforms and prostaglandin dehydrogenase in the endometrium menstrual cycle and after insertion of levonorgestrel-releasing of women using a levonorgestrel-releasing intrauterine system. *Adv Contracept* 8: 33–40.

Martinez, H., Arana, H., Gancedo, B., Larel, M, De Virgillis M. *et al.* (2010) A typical pseudotumor cerebri. *Neuroophthalmology* 34: 131–288.

McCandless, L., Gustafson, P. and Levy, A. (2007) Bayesian sensitivity analysis for unmeasured confounding in observational studies. *Stat Med* 26: 2331–2347.

Nilsson, C., Haukkamaa, M., Vierola, H. and Luukkainen, T. (1982) Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. *Clin Endocrinol* 17: 529–536.

Ratsula, K., Toivonen, J., Lahteenmaki, P. and Luukkainen, T. (1989) Plasma levonorgestrel levels and ovarian function during the use of a levonorgestrel-releasing intracervical contraceptive device. *Contraception* 39: 195–204.

Rowe, F. and Sarkies, N. (1999). The relationship between obesity and idiopathic intracranial hypertension. *Int J Obes Relat Metab Disord* 23: 54–59.

Schisterman, E., Cole, S. and Platt, R. (2009) Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* 20: 488–495.

Sheehan, J. (1982) Hormone replacement treatment and benign intracranial hypertension 284(6330): 1675–1676.