

doi: 10.13241/j.cnki.pmb.2018.19.016

帕瑞昔布联合股神经阻滞用于膝关节置换术后镇痛的效果评价 及其对患者免疫功能的影响*

何家璇 孟丽华 袁浩峥 张 勇 吴 刚[△]

(西安交通大学第二附属医院麻醉科 陕西 西安 710004)

摘要 目的:探讨帕瑞昔布联合股神经阻滞用于膝关节置换术后镇痛的效果及对患者免疫功能的影响。**方法:**选择 2016 年 10 月-2017 年 10 月我院骨科住院部收治并行单侧膝关节置换的患者 108 例,按镇痛方式分为对照组和观察组各 54 例。对照组患者采用单纯股神经阻滞,观察组采用股神经阻滞联合帕瑞昔布。比较两组静息及活动状态下术后 VAS 评分、术后膝关节 HSS 评分、不良反应的发生情况及免疫指标的变化情况。**结果:**静息及活动状态下,观察组术后 VAS 评分均明显低于对照组(P 均 <0.05),膝关节 HSS 评分显著高于对照组($P<0.05$)。两组术后不良反应的发生情况比较差异无统计学意义($P>0.05$)。手术结束时,两组 $CD4^+$ 较麻醉前均显著下降(P 均 <0.05);术后 72 h,两组 $CD4^+$ 、 $CD8^+$ 及 $CD4^+/CD8^+$ 较麻醉前均无显著差异(P 均 >0.05)。观察组术后 72 h $CD4^+$ 比对照组高($P<0.05$),而 $CD4^+/CD8^+$ 显著低于对照组($P<0.05$)。**结论:**帕瑞昔布联合股神经阻滞对膝关节置换术后镇痛临床效果好,利于保护和改善患者免疫功能,促进膝关节功能的康复。

关键词:帕瑞昔布;股神经阻滞;膝关节置换术;术后镇痛;免疫功能

中图分类号:R687.4 **文献标识码:**A **文章编号:**1673-6273(2018)19-3673-04

Evaluation of the Analgesia Effect of Parecoxib Combined with Femoral Nerve Block after Knee Replacement Operation and Its Effect on the Immune Function*

HE Jia-xuan, MENG Li-hua, YUAN Hao-zheng, ZHANG Yong, WU Gang[△]

(Anesthesiology Department, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710004, China)

ABSTRACT Objective: To explore the analgesia effect of parecoxib combined with femoral nerve block after the knee replacement operation and its effect on the immune function. **Methods:** 108 cases of patients who underwent unilateral knee replacement in our hospital from October 2016 to October 2017 were selected and divided into the control group and the observation group by analgesic method, with 54 cases in each group. Patients in the control group were treated with femoral nerve block, while patients in the observation group were treated with femoral nerve block combined with parecoxib. The VAS score, HSS score, the occurrence of adverse reactions and the changes of immune indexes were compared between the two groups. **Results:** The VAS score of resting and activity of observation group were lower than those of the control group ($P<0.05$). The HSS score of observation group was significantly higher than that of the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). At the end of the operation, the $CD4^+$ of both groups were significantly lower than those before anesthesia ($P<0.05$). There was no significant difference in the $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ between the two groups ($P>0.05$). $CD4^+/CD8^+$ was significantly lower in the observation group than that in the control group ($P<0.05$). **Conclusions:** Parecoxib combined with femoral nerve block for postoperative analgesia after knee replacement is good, it can improve the immune function of patients and promote the rehabilitation of knee function.

Key words: Parecoxib; Femoral nerve block; Knee replacement; Postoperative analgesia; Immune function

Chinese Library Classification(CLC): R687.4 **Document code:** A

Article ID: 1673-6273(2018)19-3673-04

前言

人体构造最复杂且最大的关节是膝关节,由髌骨、股骨内、外侧髁及胫骨内、外侧髁构成^[1,2],容易受到外力等因素的作用而受伤,严重时会造成功能性损伤,影响患者的日常生活和身

心健康^[3,4]。由于老年患者随着年龄的增长更容易发生钙流失,加之骨质疏松则更容易发生膝关节等其他骨损伤,越来越多的报道显示膝关节疾病已呈现出年轻化趋势^[5,6]。治疗退行性膝关节炎、类风湿性关节炎等破坏性膝关节疾病,通过关节置换可以纠正膝关节畸形,重建稳定的关节,改善膝关节功能,提高患

* 基金项目:陕西省自然科学基金项目(2014JM2-8199)

作者简介:何家璇(1980-),女,硕士,主治医师,研究方向:临床麻醉与重要脏器缺血再灌注损伤机制,E-mail: hejiaxuan_801016@163.com

△ 通讯作者:吴刚(1972-),男,硕士,副教授,研究方向:围术期脏器缺血再灌注损伤机制与保护,E-mail: wugang_1972@163.com

(收稿日期:2018-03-06 接受日期:2018-03-30)

者的生活质量和身心健康,且中远期疗效好,越来越多的患者从中受益^[7,8]。虽然膝关节置换术是治疗破坏性膝关节疾病的有效手段,但因其创伤大、出血多,导致患者术后的疼痛感强烈。若不能采取有效的镇痛处理,将会严重影响患者的生活质量和满意度^[9,10]。

股神经阻滞是临床常用的镇痛方式,能有效阻滞支配膝关节的股神经,在一定程度上能减轻术后关节的疼痛,但膝关节神经分布复杂,除股神经外还有闭孔神经、坐骨神经一起支配膝关节,仅靠股神经阻滞并不能达到良好的镇痛效果^[11,12]。帕瑞昔布一种环氧合酶-2(COX-2)特异性抑制剂,适用于骨科患者

的术后镇痛,常用作抗关节炎药中的昔布类镇痛药^[13]。本研究通过帕瑞昔布联合股神经阻滞对膝关节置换术患者进行术后镇痛,效果佳。现报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 10 月-2017 年 10 月我院骨科住院部收治并行单侧膝关节置换的患者 108 例,按镇痛方式分为对照组 54 例、观察组 54 例。两组一般资料比较无显著差异($P>0.05$),见表 1。

表 1 两组一般资料的比较($\bar{x} \pm s$)
Table 1 Comparison of the general information between the two groups($\bar{x} \pm s$)

Groups	n	Age (year)	Gender (male/female)	BMI (kg/m ²)	Side (left/right)	Time of operation (min)
Control group	54	69.6 $\pm$ 4.2	30/24	25.4 $\pm$ 2.7	25/29	77.5 $\pm$ 5.8
Observation group	54	71.2 $\pm$ 5.7	28/26	24.7 $\pm$ 2.3	22/32	76.8 $\pm$ 7.9

1.2 纳入及排除标准

纳入标准:①符合膝关节骨性关节炎诊断标准,有明确关节置换手术指征者;②疾病确诊后择期行单侧膝关节置换术治疗,手术由同一组医师完成,采用同一种假体产品;③术后入住无痛病房,采用连续股神经阻滞或联合帕瑞昔布进行治疗,并有详细记录;④患者对本研究知情且已签署知情同意书。

排除标准:①膝关节严重畸形;②依从性较差,不能配合研究;③严重心、肝、肾损害影响药物代谢;④有凝血功能障碍,周围神经病变,智力障碍、精神疾病,类风湿性膝关节炎;⑤每天摄入强阿片或类固醇类药物;⑥酗酒、药物滥用。

1.3 方法

两组患者均进行常规的膝关节置换手术。对照组患者通过单纯股神经阻滞进行镇痛,术后 0.25%罗哌卡因 25 mL 通过股神经阻滞导管注入,3 次/d,共 3 d;研究组患者采用股神经阻滞联合帕瑞昔布,于膝关节置换手术结束前 30 min、术后 12、24 及 48 h 静脉注射 40 mg 帕瑞昔布,术后 0.25%罗哌卡因 25 mL 通过股神经阻滞导管注入,3 次/d,共 3 d。

所有患者麻醉前、手术结束时、术后 24、48、72 h 五个时间点抽取外周静脉血 4.0 mL,用离心机对血浆进行分离,保存于-80℃冰箱待测。采用 COULTER EPICS XL 流式细胞仪(Beckman Coulter 公司,美国)在术前、手术结束时,术后 24、48、72 h

检测 T 淋巴细胞亚群 CD3⁺、CD4⁺、CD8⁺ 及 NK 细胞水平,计算 CD4⁺/CD8⁺ 值。

1.4 观察指标

1.4.1 镇痛效果 利用视觉模拟量表 (visual analogue scale, VAS)评估患者静息状态下术后 12、24、48 h 及活动状态下术后 24、48、72 h 的疼痛状况。0 分代表无痛感,1-3 分代表有轻度疼痛症状,4-7 分代表有中度疼痛感,8-10 分代表疼痛感严重^[14]。

1.4.2 膝关节功能 利用 HSS 膝关节功能评分^[15]对患者术前、术后 24、48、72 h 膝关节功能进行评价。85-100 分、70-84 分、60-69 分、小于 60 分分别代表优、良、中、差。

1.4.3 不良反应发生情况 记录患者术后不良反应的发生情况。

1.4.4 免疫功能 观察两组患者在麻醉前,手术结束时,术后 24、48、72 h 时 T 淋巴细胞亚群 CD4⁺、CD8⁺ 水平,计算 CD4⁺/CD8⁺ 值。

2 结果

2.1 两组术后镇痛效果的比较

静息状态下,观察组术后 12、24、48 h VAS 评分均显著低于对照组(P 均 <0.05),见表 2。活动状态下,观察组术后 24、48、72 h VAS 评分均低于对照组(P 均 <0.05),见表 3。

表 2 两组术后静息状态下不同时间疼痛 VAS 评分的比较($\bar{x} \pm s$)

Table 2 Comparison of the VAS scores of resting pain between two groups at different time points($\bar{x} \pm s$)

Group	n	12 h	24 h	48 h
Control group	54	4.1 $\pm$ 0.74	3.7 $\pm$ 0.49	3.2 $\pm$ 0.52
Observation group	54	3.8 $\pm$ 0.67*	3.1 $\pm$ 0.61*	2.7 $\pm$ 0.33*

Note: compared with the control group, * $P<0.05$.

2.2 两组膝关节功能改善情况的比较

手术前,两组膝关节 HSS 评分比较无显著差异($P>0.05$)。手术后 24、48、72 h,观察组膝关节 HSS 评分均显著高于对照组(P 均 <0.05),见表 4。

2.3 两组术后不良反应发生情况的比较

两组镇痛过程中无严重不良反应的发生,观察组有 3 例发生恶心/呕吐症状,对照组有 4 例发生此症状,两组术后不良反应的发生情况比较无统计学差异($P>0.05$)。

表 3 两组术后活动状态下不同时间疼痛 VAS 评分($\bar{x} \pm s$)Table 3 Comparison of the VAS scores of activity pain between two groups at different time points($\bar{x} \pm s$)

Groups	n	12 h	24 h	48 h
Control group	54	4.4 $\pm$ 0.69	3.9 $\pm$ 0.51	3.6 $\pm$ 0.46
Observation group	54	3.9 $\pm$ 0.58*	3.3 $\pm$ 0.37*	2.9 $\pm$ 0.35*

Note: compared with the control group, *P<0.05.

表 4 两组不同时间点膝关节 HSS 评分的比较($\bar{x} \pm s$)Table 4 Comparison of the HSS scores between the two groups at different time points($\bar{x} \pm s$)

Groups	n	Before the operation	24 h	48 h	72 h
Control group	54	43.6 $\pm$ 5.8	56.3 $\pm$ 5.4	64.8 $\pm$ 5.9	72.3 $\pm$ 6.9
Observation group	54	45.5 $\pm$ 6.1	64.2 $\pm$ 5.9*	79.6 $\pm$ 6.8*	86.4 $\pm$ 7.5*

Note: compared with the control group, *P<0.05.

2.4 两组免疫功能的比较

两组麻醉前 CD4⁺、CD8⁺ 及 CD4⁺/CD8⁺ 比较无显著差异(P 均 >0.05)。手术结束时,两组 CD4⁺ 较麻醉前均显著下降(P 均

<0.05); 术后 72 h, 两组 CD4⁺、CD8⁺ 及 CD4⁺/CD8⁺ 较麻醉前均无显著差异 (P 均 >0.05)。观察组术后 72 h CD4⁺ 比对照组高 (P<0.05), 而 CD4⁺/CD8⁺ 显著低于对照组(P<0.05), 见表 5。

表 5 两组不同时间点免疫指标的比较($\bar{x} \pm s$)Table 5 The comparison of immune parameters between two groups at different time points($\bar{x} \pm s$)

Groups	Before anesthesia	At the end of the operation	24 h	72 h
Control group(n=54)				
CD4 ⁺	34.9 $\pm$ 4.2	28.2 $\pm$ 3.9*	31.6 $\pm$ 3.7*	34.1 $\pm$ 3.4
CD8 ⁺	24.6 $\pm$ 3.8	23.3 $\pm$ 4.2	24.5 $\pm$ 3.6	24.7 $\pm$ 3.4
CD4 ⁺ /CD8 ⁺	1.4 $\pm$ 0.3	1.3 $\pm$ 0.3	1.2 $\pm$ 0.3*	1.4 $\pm$ 0.5
Observation group(n=54)				
CD4 ⁺	35.2 $\pm$ 5.3	28.8 $\pm$ 4.7*	33.1 $\pm$ 3.8*#	35.7 $\pm$ 4.2#
CD8 ⁺	24.7 $\pm$ 3.1	23.5 $\pm$ 3.6	25.9 $\pm$ 4.1	26.1 $\pm$ 4.5
CD4 ⁺ /CD8 ⁺	1.5 $\pm$ 0.4	1.4 $\pm$ 0.5	1.2 $\pm$ 0.4*	1.2 $\pm$ 0.3*#

Note: compared with before anesthesia, *P<0.05; compared with control group, #P<0.05.

3 讨论

膝关节置换术后患者常伴有膝关节周围疼痛,对患者术后膝关节功能的恢复和生活质量产生很大影响^[16-18],术后镇痛方案的选择会影响到患者的疼痛感、早期的功能锻炼及康复进程。膝关节置换术后镇痛方法有很多,FNB 是近几年临床使用较多的新型镇痛方法。有研究显示 FNB 能显著缓解患者术后静息痛、运动痛,但膝关节由股神经、坐骨神经、闭孔神经和骨外侧皮神经共同参与支配,故 FNB 的镇痛范围存在一定的局限性,常需要联合其他方式共同镇痛^[19,20]。帕瑞昔布是临床上常见的骨科手术患者术后镇痛药物,具有镇痛和消炎的作用。有研究显示帕瑞昔布起效快,对胃肠道和血小板影响小且不具有成瘾性,但单独用于创伤较大的手术是远远不够的^[21,22]。因此,本研究将股神经阻滞与帕瑞昔布联合应用于膝关节置换术后镇痛,一方面探究二者联合应用对于术后镇痛的疗效,另一方面对于镇痛疗效的反应机制从免疫功能方面进行探讨。

帕瑞昔布是环氧合酶-2(COX-2)抑制剂,属于非甾体类抗炎镇痛药。COX-2 参与疼痛、炎症及相关递质的合成,而帕瑞昔布可以通过抑制 COX-2 活化而阻断花生四烯酸转换为前列腺素的合成过程,减少炎症递质产生进而起到镇痛消炎的作用^[23,24]。本研究结果显示静息状态下,观察组术后 12、24、48 h VAS 评分均低于对照组;活动状态下,观察组术后 24、48、72 h VAS 评

分均明显低于对照组,与帕瑞昔布的镇痛消炎机制有关。本研究结果还显示观察组术后 24、48、72 h 膝关节 HSS 评分显著高于对照组,两组术后不良反应的发生情况比较无显著差异。Zhu Y Z 等^[25] 研究显示股神经阻滞联合间断静脉注射帕瑞昔布,可安全、有效地缓解老年病人膝关节置换术后疼痛,有助于术后关节功能的康复,与本研究结果一致。以上结果说明帕瑞昔布有良好的镇痛效果,能够有效缓解膝关节置换术后患者的疼痛。

术后疼痛、手术创伤等会影响患者的免疫力,免疫功能下降会影响患者的尽早康复^[26]。细胞免疫功能的评判常以 T 淋巴细胞亚群作为评价指标,成熟的 T 细胞随血液流至外周免疫器官,也可经组织液、外周血、淋巴管等进行再循环发挥作用^[27]。CD4⁺ 和 CD8⁺ 不能同时大量表达于成熟 T 淋巴细胞,所以常用 CD4⁺/CD8⁺ 区分成熟的 T 淋巴细胞^[28]。本研究结果显示手术结束时、术后 24 h 两组 CD4⁺ 较麻醉前均显著降低,术后 24 h 两组 CD4⁺/CD8⁺ 较麻醉前均显著降低,说明手术创伤及术后的疼痛降低了患者的免疫力。本研究结果显示术后 72 h 观察组 CD4⁺/CD8⁺ 显著低于对照组,与 Li D F^[29] 的研究结果一致。以上结果提示帕瑞昔布能够改善膝关节置换术后患者的免疫功能。

综上所述,帕瑞昔布联合股神经阻滞对膝关节置换术后镇痛临床效果好,利于保护和改善患者免疫功能,促进膝关节功能的康复。

参 考 文 献(References)

- [1] Wylde V, Trela-Larsen L, Whitehouse M R, et al. Preoperative psychosocial risk factors for poor outcomes at 1 and 5 years after total knee replacement[J]. *Acta Orthop*, 2017, 88(5): 530-536
- [2] Gromov K, Kjærsgaard A P, Revald P, et al. Feasibility of outpatient total hip and knee arthroplasty in unselected patients[J]. *Acta Orthop*, 2017, 88(5): 516-521
- [3] Bugada D, Allegri M, Gemma M, et al. Effects of anaesthesia and analgesia on long-term outcome after total knee replacement: A prospective, observational, multicentre study [J]. *Eur J Anaesthesiol*, 2017, 34(10): 665-672
- [4] Rutherford R W, Jennings J M, Dennis D A. Enhancing recovery after total knee arthroplasty [J]. *Orthop Clin North Am*, 2017, 48 (4): 391-400
- [5] Badawy M, Fenstad A M, Bartz J C A, et al. Hospital volume and the risk of revision in Oxford unicompartmental knee arthroplasty in the Nordic countries-an observational study of 14,496 cases [J]. *BMC Musculoskelet Disord*, 2017, 8(1): 388
- [6] Sun E C, Bateman B T, Memtsoudis S G, et al. Lack of association between the use of nerve blockade and the risk of postoperative chronic opioid use among patients undergoing total knee arthroplasty: evidence from the marketscan database [J]. *Anesth Analg*, 2017, 125(3): 999-1007
- [7] Agodi A, Auxilia F, Barchitta M, et al. Risk of surgical site infections following hip and knee arthroplasty: results of the ISChIA-GISIO study[J]. *Ann Ig*, 2017, 29(5): 422-430
- [8] Bade M J, Struessel T, Dayton M, et al. Early high-intensity versus low-intensity rehabilitation after total knee arthroplasty: a randomized controlled trial [J]. *Arthritis Care Res (Hoboken)*, 2017, 69 (9): 1360-1368
- [9] Koh C K, Zeng I, Ravi S, et al. Periprosthetic joint infection is the main cause of failure for modern knee arthroplasty: an analysis of 11,134 knees[J]. *Clin Orthop Relat Res*, 2017, 475(9): 2194-2201
- [10] Kwong L M, Turpie A G G, Tamayo S, et al. A post-marketing assessment of major bleeding in total hip and total knee replacement surgery patients receiving rivaroxaban [J]. *Curr Med Res Opin*, 2017, 33(9): 1717-1723
- [11] Seo S S, Kim O G, Seo J H, et al. Comparison of the effect of continuous femoral nerve block and adductor canal block after primary total knee arthroplasty[J]. *Clin Orthop Surg*, 2017, 9(3): 303-309
- [12] Tang Y, Tang X, Wei Q, et al. Intrathecal morphine versus femoral nerve block for pain control after total knee arthroplasty: a meta-analysis[J]. *J Orthop Surg Res*, 2017, 12(1): 125
- [13] Lu J, Chen G, Zhou H, et al. Effect of parecoxib sodium pretreatment combined with dexmedetomidine on early postoperative cognitive dysfunction in elderly patients after shoulder arthroscopy: A randomized double blinded controlled trial [J]. *J Clin Anesth*, 2017, 30(41): 30-34
- [14] Voutilainen A, Pitkääho T, Kvist T, et al. How to ask about patient satisfaction? The visual analogue scale is less vulnerable to confounding factors and ceiling effect than a symmetric Likert scale [J]. *J Adv Nurs*, 2016, 72(4): 946-957
- [15] Zhao W, Li M, Wang L, et al. The correlation between shifting of the patient's gravity center position and the degree of recovering joint function after total knee arthroplasty [J]. *Zhonghua Wai Ke Za Zhi*, 2015, 53(4): 285-288
- [16] MacDonald D W, Chen A F, Lee G C, et al. Fretting and corrosion damage in taper adapter sleeves for ceramic heads: a retrieval study [J]. *J Arthroplasty*, 2017, 32(9): 2887-2891
- [17] Loyd B J, Jennings J M, Falvey J R, et al. Magnitude of deformity correction may influence recovery of quadriceps strength after total knee arthroplasty[J]. *J Arthroplasty*, 2017, 32(9): 2730-2737
- [18] De C J H, Aiello P M, Warrity O K, et al. Effectiveness of bupivacaine liposome injectable suspension for postoperative pain control in total knee arthroplasty: a prospective, randomized, double blind, controlled study[J]. *J Arthroplasty*, 2017, 32(9S): S268-S271
- [19] Al W A M. Evaluation of pain during endovenous laser ablation of the great saphenous vein with ultrasound-guided femoral nerve block [J]. *Vasc Health Risk Manag*, 2017, 13(13): 305-309
- [20] Fei D, Ma L P, Yuan H P, et al. Comparison of femoral nerve block and fascia iliaca block for pain management in total hip arthroplasty: A meta-analysis[J]. *Int J Surg*, 2017, 14(46): 11-13
- [21] Nenicu A, Gu Y, Körbel C, et al. Combination therapy with telmisartan and parecoxib induces regression of endometriotic lesions[J]. *Br J Pharmacol*, 2017, 174(16): 2623-2635
- [22] Li X, Liu J, Zhou M, et al. Parecoxib sodium pretreatment reduces myoclonus after etomidate: A prospective, double-blind, randomized clinical trial[J]. *Int J Clin Pharmacol Ther*, 2017, 55(7): 601-605
- [23] Mu D L, Zhang D Z, Wang D X, et al. Parecoxib supplementation to morphine analgesia decreases incidence of delirium in elderly patients after hip or knee replacement surgery: a randomized controlled trial [J]. *Anesth Analg*, 2017, 124(6): 1992-2000
- [24] Diaz B E, Torres G A, Essex M N, et al. Parecoxib provides analgesic and opioid-sparing effects following major orthopedic surgery: a subset analysis of a randomized, placebo-controlled clinical trial[J]. *Pain Ther*, 2017, 6(1): 61-72
- [25] Zhu Y Z, Yao R, Zhang Z, et al. Parecoxib prevents early postoperative cognitive dysfunction in elderly patients undergoing total knee arthroplasty: A double-blind, randomized clinical consort study [J]. *Medicine (Baltimore)*, 2016, 95(28): e4082
- [26] Gryglewski A, Szczepanik M. The Effect of surgical stress on postoperative $T\alpha\beta$ and $T\gamma\delta$ cell distribution [J]. *Immunol Invest*, 2017, 46 (5): 481-489
- [27] Ma K, Ma P, Lu H, et al. Fentanyl suppresses the survival of CD4⁺T Cells isolated from human umbilical cord blood through inhibition of IKKs-mediated NF- κ B activation [J]. *Scand J Immunol*, 2017, 85(5): 343-349
- [28] Guo S Y, Ding Y J, Li L, et al. Correlation of CD4⁺, CD25⁺, Foxp3⁺treg with the recovery of joint function after total knee replacement in rats with osteoarthritis[J]. *Genet Mol Res*, 2015, 14(3): 7290-7296
- [29] Li D F. Effect of continuous femoral nerve block combined with general anesthesia on immune function in elderly patients after knee joint replacement [J]. *Journal of Qiqihar University of Medicine*, 2016, 37 (26): 3264-3266
- [30] Inthigood N, Lertbunnaphong T, Jaishuen A. Efficacy of a single 40 mg intravenous dose of parecoxib for postoperative pain control after elective cesarean delivery: A double-blind randomized placebo-controlled trial[J]. *J Obstet Gynaecol Res*, 2017, 43(1): 92-99