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Analysis of Interleukin-8 and Interleukin-6 Levels Post Urinary Catheter Insertion in Pelvic Organ Prolapse Surgery

Fadhilah Ramadhani Anwar[1*], Imam Ahmadi Farid[1], St. Nur Asni[1], Trika Irianta[1], Anggrainy D. Kouwagam[1], Susiawaty[1]

[1]Department of Obstetric and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

***Corresponding Author:**

Fadhilah Ramadhani Anwar

Department of Obstetric and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia, Jl. Perintis Kemerdekaan KM 10, Tamalanrea 90245, Makassar, South Sulawesi, Indonesia

Email ID: fadhilahraobgynjan21@gmail.com

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ABSTRACT

Background: Pelvic organ prolapse (POP) can cause pressure on the urethra, causing urinary problems and increasing the risk of urinary tract infection (UTI). Interleukin (IL)-8 and IL-6 are cytokines produced in response to bacterial infection but have been reported inconsistently in UTI. This study aims to analyze the relationship between urinary IL-8 and IL-6 levels with UTI before and after urinary catheter insertion in POP surgery.

Methods: This study is an observational study in women who will undergo POP surgery at Wahidin Sudirohusodo Hospital and Network Hospital from March to October 2024. Urine samples of patients were taken before catheter insertion in POP surgery and during catheter removal after pelvic organ surgery. IL-8 and IL-6 levels were measured using ELISA kits. Statistical analysis used the Mann Whitney test and Kruskal Wallis test.

Results: Total of 44 women were collected, most of whom were 50-70 years old, multiparous and obese. Urinary IL-8 and IL-6 levels were significantly different before and after urinary catheter insertion in patients undergoing POP surgery ($p < 0.05$). Changes in IL-8 levels after urinary catheter insertion were greater than changes in IL-6 levels after urinary catheter insertion ($p < 0.05$). IL-6 levels did not differ significantly based on age, parity and BMI ($p > 0.05$). Urinary IL-8 levels were significantly different based on age and parity ($p < 0.05$), not significantly different based on BMI ($p > 0.05$).

Conclusion: Urinary IL-8 and IL-6 levels increased after urinary catheter insertion in POP surgery.

Keyword: *interleukin-6, pelvic organ prolapse, urine, interleukin-8*

1. INTRODUCTION

Pelvic organ prolapse (POP) surgery is a surgical procedure performed to repair the muscles and supporting tissues in the pelvis that are weakened, causing the pelvic organs to go down. The surgery aims to remove these organs and strengthen the muscles and their supporting tissues (1). In POP surgery, a catheter is given after surgery to help the patient pass urine because there may be swelling or pain in the pelvic area that makes it difficult to urinate normally (2). Urinary catheterization is also performed to evaluate urine output and avoid urine retention. However, the administration of the catheter must be done with caution and should be avoided for too long use of more than 3 days because it can cause urinary tract infections and damage the tissues inside the urinary tract (3).

Pelvic prolapse, also known as genital prolapse, refers to the descent of pelvic organs due to the weakening of one or more layers of the pelvic floor. This weakening can affect the anterior, apical, or posterior pelvic walls, leading to the protrusion of the vaginal wall as a result of pressure on the pelvic organs. Research indicates that between 11% and 14% of women will require medical intervention for prolapse at some point in their lives (4). Approximately 40% of individuals with prolapse experience urinary difficulties, which increases the likelihood of urinary tract infections (UTIs). Anterior prolapse, specifically cystocele, is the type most closely associated with UTIs; however, rectocele or posterior prolapse, can also exert significant pressure on the urethra, resulting in urinary complications and heightening the risk of UTIs (5). Understanding

which pelvic wall is affected is crucial for developing an appropriate treatment strategy. The POP Quantification system, the most recent scoring method for prolapse, categorizes the condition into four stages, with each stage reflecting increasing severity. Surgical intervention is recommended for symptoms of prolapse that lead to dyspareunia or a sensation of a foreign body, as well as for bladder obstruction frequently associated with UTIs (6). Conversely, when prolapse does not contribute to urinary issues, it does not elevate the risk of UTIs. A study conducted in southeastern Nigeria found that 75% of women with pelvic prolapse had asymptomatic bacteriuria, with treatment for this condition being warranted only in cases of pregnancy or before urinary tract surgery (7)

Previous research has identified several cytokines as inflammatory biomarkers linked to UTIs, particularly interleukin (IL)-8 and IL-6. Both IL-8 and IL-6 are produced in response to bacterial infections and play critical roles as inflammatory mediators (8). Prior studies have shown that levels of IL-6 and IL-8 in urine and serum are elevated in patients with UTIs compared to controls. While some studies reported significantly higher urine and serum levels of IL-8 in UTI patients relative to controls, they found no significant difference in IL-6 levels between the two groups (Lyu et al., 2022). Previous studies have reported that urine and serum levels of IL-8 and IL-6 are higher in UTIs than in controls. Different results reported, the urine and serum IL-8 levels were significantly higher in UTIs than in controls, but no significant difference in IL-6 levels between UTIs and controls was found (9). In addition, research related to the measurement of IL-8 and IL-6 levels due to the use of urinary catheters after POP surgery has never been done before. This study is interested in clarifying the results regarding the comparison of IL-8 and IL-6 levels between before and after POP surgery. The increase IL-8 and IL-6 levels after catheterization makes these cytokines potentially inflammatory biomarkers that are side effects of POP surgery after catheterization (10). This research is important because finding inflammatory biomarkers in postoperative patients can be useful as a future policy to determine strategies for the management of POP surgery and optimize the results of POP surgery.

This study aims to analyze the relationship between urinary IL-8 and IL-6 levels with UTI before and after urinary catheter insertion in POP surgery

2. MATERIALS AND METHODS

The cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital and the Network Hospital from March to October 2024. The number of respondents who meet the inclusion criteria can be met. The population in this study is all female patients who will undergo the POP surgery. The minimum sample size for each group is 44 people for each patient before and after the installation of the urinary catheter. Samples were taken from the sample population by consecutive sampling, namely each sample that met the inclusion and exclusion criteria according to the order of arrival until the number of samples was met.

Patients who will undergo POP surgery have routine urine tests to confirm the absence of urinary tract infections before surgery. Urine samples were collected and analyzed in accordance with the established protocols at our institution. The method of urine collection utilized with the clean midstream technique before urinary catheterization and sample obtained via catheterization post intervention. The collection was conducted using the BD Vacutainer Urine Collection System (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), which included Vacutainer urine collection cups and urinalysis tubes. Following collection, the samples were maintained at room temperature and subsequently transported to the laboratory and microbiology departments. Urine diagnostics, including both urinalysis and automated analysis, were conducted within one hour of sample arrival. Post-analysis, the urine samples were refrigerated at approximately 7°C. Any residual materials from urine and plasma (the latter collected in lithium-heparin tubes) were stored at −80°C within a 24-hour timeframe for future biomarker analyses.

All biomarkers were analyzed in a single batch. The levels of IL-8 and IL-6 were quantified using the BioLegend LEGEND MAX™ Human IL-8 and IL-6 ELISA Kit. The assay's lower limit of detection was 4.4 pg/mL for IL-8 and 1.6 pg/mL for IL-6. Assessment of subsequent recombinant cytokines and chemokines at 50 ng/mL revealed no cross-reactivity.

3. RESULTS

There were 45 patients, of which there was 1 patient who dropped out because the patient died and could not participate in the study until the end. The characteristics of the subjects of this study are presented in Table 1.

Table 1 shows that most of the subjects of this study are 50-70 years old 35 years old (79.5%). Based on parity, most of the subjects of this study were multipara 21 (47.7%) and based on BMI, most of the subjects of this study were obese 37 (84.1%). The results of the analysis of factors related to changes in urinary IL-8 levels after urinary catheter insertion in patients undergoing POP surgery are presented in Table 2.

Based on Table 2, it shows that there is a significant difference ($p < 0.05$) in changes in urine IL-8 levels based on age $p = 0.037$ and parity $p = 0.039$. Meanwhile, based on BMI, no significant difference was found ($p > 0.05$). The results of the analysis of factors related to changes in urinary IL-6 levels after urinary catheter insertion in patients undergoing POP surgery are presented in Table 3.

Based on Table 3. it was shown that there was no significant difference ($p < 0.05$) IL-6 levels based on age, parity and BMI. The results of the comparison of urinary IL-8 and IL-6 levels between before and after urinary catheter insertion in patients undergoing POP surgery are presented in Table 4.

Based on Table 4, it was shown that there was a significant difference ($p < 0.05$) in urine IL-8 and IL-6 levels before and after urinary catheter insertion in patients undergoing POP surgery ($p < 0.01$). Urinary IL-8 and IL-6 levels after urinary catheter insertion at POP surgery are higher than before urinary catheter insertion. Thus, urinary catheter insertion in POP surgery increases urinary IL-8 and IL-6 levels. This table also shows that there is a significant difference ($p < 0.05$) in IL-6 levels with changes in IL-8 levels after urinary catheter insertion in patients undergoing POP surgery. The change in IL-8 levels after urinary catheter insertion was greater than the change in IL-6 levels after urinary catheter insertion.

Table 1. Characteristics of participants

Characteristic	n (%)
Age (years)	
< 50	3 (6.8)
50–70	35 (79.5)
> 70	6 (13.7)
Parity	
Primipara	3 (6.8)
Multipara	21 (47.7)
Grand multipara	20 (45.5)
BMI	
Normal	1 (2.3)
Overweight	6 (13.6)
Obese	37 (84.1)

Table 2. Results of analysis of factors related to changes in IL-8 levels after urinary catheter insertion

Variable	Change in IL-8 levels (ng/mL) Mean ± SD	*p-value*
Age (years)		
< 50	565.44 ± 969.06	
50–70	196.80 ± 231.88	0.037*
> 70	34.46 ± 47.91	
Parity		
Primipara	277.50 ± 171.01	
Multipara	302.46 ± 421.56	0.039*
Grand multipara	80.34 ± 87.56	
BMI		
Normal	80.09 ± 0.00	
Overweight	189.22 ± 182.11	0.952
Obese	204.74 ± 337.54	

Table 3. Results of analysis of factors related to changes in IL-6 levels after urinary catheter insertion

Variable	Change in IL-6 levels (ng/mL) Mean ± SD	*p-value*
Age (years)		
< 50	487.45 ± 812.01	
50–70	37.93 ± 39.87	0.091
> 70	19.75 ± 46.20	
Parity		
Primipara	38.66 ± 17.24	

Multipara	107.71 ± 305.36	0.252
Grand multipara	26.53 ± 33.45	
Normal		
Overweight	82.49 ± 0.00	
Obese	54.40 ± 56.78	0.182
Normal	67.56 ± 232.10	

Table 4. Results of comparison of IL-8 and IL-6 levels between before and after urinary catheter insertion in patients undergoing POP surgery

Variable	Before	After	*p-value*
	Mean ± SD	Mean ± SD	
IL-6 levels (ng/mL)	8.06 ± 12.06	74.16 ± 212.84	< 0.001*
IL-8 levels (ng/mL)	8.06 ± 23.10	216.28 ± 312.18	< 0.001*

4. DISCUSSION

In this study, most of the patients who underwent POP surgery were 50-70 years old. In previous studies, the prevalence of POP surgery ranged from 1.5 to 1.8 per 1,000 women per year and peaked in women aged 60–69 years. Women over the age of 50 are stated to have the largest prevalence of POP worldwide (11). About 11% of American women have had surgery before the age of 79. Furthermore, existing literature indicates that POP is highly prevalent among women aged over 40, particularly in elderly and postmenopausal populations, with prevalence estimates ranging from 41% to 50%.(12).

Aging is related to a decrease in skeletal muscle fibers and muscle strength. Levator ani is a skeletal muscle that helps build and maintain the support of the pelvic organs. The pelvic floor, formed by the levator, can be thought of as a "bowl" of varying depths and volumes that is cut off on one side by the urogenital hiatus. Aging leads to a weakening of the levator, which leads to "sagging," or deepening, of the levator bowl (13). This, in turn, creates an increase in space in the pelvis, which allows the descent of the pelvic organs. The incidence of POP by age can also be explained in relation to menopause. Hormonal changes during menopause result in reduced systemic estrogen levels, affecting collagen integrity in pelvic organs (14). The influence of estrogen on tissues is contingent upon both its concentration and receptor expression. Estrogen and its receptors regulate genes responsible for extracellular matrix growth factors. During menopause, alterations in collagen concentration and quality, as well as modifications in connective tissue morphology, serve as indicators of estrogen's role in collagen metabolism, which is implicated in the pathogenesis of POP (15). The levels of collagen within the vaginal tissue are influenced by the equilibrium between collagen synthesis and degradation processes. Estrogen receptors are found in diverse tissues, including connective tissues, levator ani muscle, vaginal mucosa, utero-sacral ligament, and bladder smooth muscle. The utero-sacral and cardinal ligaments are crucial for pelvic organ support. In postmenopausal women with POP, lower serum estrogen and estrogen receptor levels in pelvic floor ligaments were observed compared to those without POP (16,17).

This study was conducted in the age group of <50, 50–70 and >70 years. This is because with the increase of age groups (<50, 50–70 and >70 years), IL-8 and IL-6, and TNF-α levels increase (18). The functionality of the immune system typically diminishes with advancing age, a phenomenon referred to as immunosenescence. This decline is elucidated through three primary theoretical frameworks: the autoimmune theory, which posits a reduced capacity to differentiate between pathogenic entities and normal tissues; the immune deficiency theory, which suggests a decrease in the overall efficacy of the immune response; and the immune dysregulation theory, which highlights regulatory imbalances among various components of the immune system. Immunosenescence is a multifaceted process characterized by numerous alterations, including the dysfunction of specific cell types such as lymphocytes, natural killer cells, neutrophils, monocytes, regulatory B and T cells. These alterations lead to heightened susceptibility to infectious diseases (19). They also affect vaccination efficacy and elevate the incidence of specific diseases. Additionally, they are linked to chronic pro-inflammatory states associated with non-communicable diseases such as neurodegenerative and cardiovascular disorders, diabetes, cognitive decline, and physical frailty (20).

The results of the study showed that most of the patients who underwent POP surgery were multiple. Grand multipara (women who have given birth to 5 or more children) are more at risk of experiencing POP compared to women with fewer children. Repeated pregnancies and deliveries damage the muscles and ligaments of the sphincter that do not fully regain their strength and elasticity (21).

In this study, the majority of patients undergoing POP surgery presented with obesity. Obesity serves as a significant risk factor for POP. It has a direct impact on the manifestation of POP symptoms. Increased intraabdominal pressure, nerve

injury, and associated comorbidities in obese women exacerbate pelvic floor dysfunction. Elevated intraabdominal pressure imposes excessive stress on pelvic structures, notably the pudendal nerve (22). In obese women, heightened intra-abdominal pressure leads to fascia and pelvic floor muscle weakening, precipitating POP. Comorbid conditions associated with obesity, such as diabetes mellitus, further impair tissue characteristics due to neuropathy, genetic predispositions, and joint hypermobility (23).

The results of this study showed that there was an increase in urinary IL-8 and IL-6 levels after urinary catheter insertion in POP surgery. An increase in urinary levels of IL-8 and IL-6 after urinary catheter insertion indicates inflammation (24). This is as stated that both IL-6 and IL-8 have been shown to play an important role in the initiation and enlargement of the inflammatory response to infection. IL-8 and IL-6 are the initial cytokines identified in urine post-infection. These cytokines are generated in reaction to bacterial infections and are key mediators of inflammation (25).

In this study, most postoperative POP patients showed positive urine leukocytes indicating the presence of a bacterial infection in the urinary system. This is because one of the inflammations that can occur after POP surgery is the occurrence of UTIs even though in this study, the increase in IL-8 and IL-6 levels does not specifically describe the occurrence of UTIs. IL-6 is secreted in response to bacterial infections whereas IL-8 is secreted by monocytes, endothelial cells and neutrophils in response to IL-1 and tumor necrosis factor-α. During infection and inflammation, many cells begin to form cytokines that digest minor and soluble proteins. During UTIs, a series of events occur that lead to microbial control and clearance starting with the activation of Toll-like receptors (TLRs). The activation of TLR4 by bacterial lipopolysaccharides elicits a robust pro-inflammatory cytokine response, including IL-8 and its murine functional equivalents, C-X-C Motif Chemokine Ligand (CXCL)1 and CXCL5. This response serves to recruit neutrophils to the site of infection, while IL-6 plays a critical role in promoting mucosal immunoglobulin A production and further inflammatory signaling pathways.

UTIs can occur after urinary catheter insertion because there is a development of biofilms in the urine catheter, which provides a favorable environment for bacterial proliferation and invasion (26). The proximity of the urethra to the intestine makes colonization by uropathogenic Escherichia coli is frequent, especially in patients who are fitted with catheters. The development of biofilm on the catheter's surface is the primary factor contributing to bacteriuria. The process of biofilm formation initiates immediately following catheter insertion, as microorganisms adhere to the conditioning layer of host proteins that develops on the catheter's surface. The bacteria are typically sourced from the periurethral region or ascend through drainage channels subsequent to the colonization of drainage pockets. Microorganisms residing within biofilms exist in an environment that offers substantial protection against antimicrobial agents and the host's immune responses.

The limitations of this study include the only examination of IL-8 and IL-6 levels in urine samples, without analyzing the urine culture. Additionally, the number of subjects in this study was limited and small. Furthermore, this study did not specifically determine whether the increase in IL-8 and IL-6 8 was caused by urinary tract infections in patients following POP surgery or by other factors.

5. CONCLUSION

This study demonstrates a statistically significant increase in urinary IL-8 and IL-6 levels following urinary catheter insertion in patients undergoing POP surgery. Furthermore, alterations in urinary IL-8 levels exhibit a correlation with age and parity, with the most pronounced changes observed in the 50-70 year age group and in primiparous individuals. Consequently, the assessment of urinary inflammatory markers, specifically IL-8 and IL-6, may serve as a potential indicator of localized inflammatory response subsequent to urinary catheterization in this patient population.

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