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RESEARCH

SURGICAL STRESS RESPONSE IN HOLMIUM LASER ENUCLEATION OF THE PROSTATE VERSUS TRANSURETHRAL RESECTION OF THE PROSTATE: A PROSPECTIVE NON-RANDOMIZED STUDY

Abstract

Aim: To compare immunoinflammatory markers and the surgical stress response in patients undergoing conventional transurethral resection of the prostate (TURP) or holmium laser enucleation of the prostate (HoLEP).

Materials and Methods: Patients with the diagnosis of benign prostate hyperplasia who needed surgical treatment were enrolled in either TURP or HoLEP surgery. Two consecutive cohorts of 25 patients in each group were non-randomly recruited based on prostate volume. Interleukin-6, C-reactive protein, tumor necrosis factor alpha, white blood cell count, neutrophil-to-lymphocyte ratio, CD4+/CD8+ ratio, and adrenaline and cortisol levels were determined at three different times: before the operation, immediately afterward, and on postoperative day 1. Operation durations, lengths of in-hospital stays, and postoperative pain scores were also assessed.

Results: The mean age was 63.1 ± 6.7 years. Interleukin-6 and C-reactive protein values were statistically higher in both groups at postoperative day 1 than preoperatively ($p < 0.05$). Interleukin-6 and C-reactive protein levels were significantly higher in the TURP at postoperative day 1 than HoLEP ($p < 0.05$). The operation duration in the TURP group was significantly shorter than in the HoLEP. The length of hospital stay was shorter in the HoLEP ($p < 0.05$). There was less postoperative pain in the HoLEP ($p < 0.05$).

Conclusion: This study shows that surgical stress response is attenuated in patients undergoing HoLEP surgery in comparison with patients receiving TURP surgery.

Keywords: C-Reactive Protein; Hormones; Interleukin-6; Minimally Invasive Surgical Procedures; Transurethral Resection of Prostate.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common illness causing significant difficulties in aging men worldwide and resulting in bladder outlet obstruction (1). The prevalence of BPH has increased in recent years in line with the aging population. An autopsy study reported that 50% and 75% of men have histological evidence of BPH in the fifth and eighth decades of life, respectively, with approximately half of them presenting with clinically significant symptoms (2). Surgery is the most effective treatment for BPH, and at least one in every five men presenting with symptoms eventually undergo surgery (3).

Conventional transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP) are the recommended endoscopic surgical techniques for the minimally invasive management of BPH (4). For more than 70 years, TURP has been utilized in the surgical treatment of BPH. It is the most used technique for the treatment of BPH and is regarded as the gold standard of surgical therapy for BPH involving prostates weighing less than 80 g (5). The use of high-temperature electric resection technology in TURP produces heat injury to the surrounding tissue and increases perioperative complications. Technological developments such as using bipolar electrodes, microprocessor-controlled units, and training have all contributed to reducing perioperative complications of TURP. However, transfusion, transurethral resection syndrome, clot retention, urinary tract infection, urinary retention, urethral strictures, and death are still among the reported complications of TURP (4). TURP is also associated with a longer operation time, increased blood loss, and a higher complication rate in large-volume prostates (> 80 g) (6). As a result, open surgery or HoLEP remain the surgical recommendations for the treatment of BPH in prostates weighing more than 80 g (5). HoLEP, an alternative to open surgery, does not produce thermal injury and is beneficial for reducing surgical trauma and incidence of the corresponding complications.

In recent years, many clinical studies have examined the clinical outcomes of patients undergoing TURP or HoLEP surgery. However, little is known about the effects of these two surgical techniques on surgical stress and immune functions. To the best of our knowledge, there have been no studies focusing on the effects of HoLEP or TURP surgery on postoperative immune functions. The objective of the present study was therefore to compare the systemic inflammatory markers and surgical stress response in patients undergoing HoLEP or TURP surgery.

MATERIALS AND METHODS

Two consecutive cohorts of patients with BPH who received surgical treatment under general anesthesia at Adana City Education and Research Hospital between February 2020 and May 2021 were enrolled in this non-randomized prospective study (Chictr.org/cn,ChiCTR-TRC- NCT05108662). The study was approved by the Institutional Review Board (Jan-2020, Ref 708-49) and conducted in accordance with the principles of the Helsinki Declaration.

The patients were assigned to either HoLEP or TURP surgery based on the volume of their prostate. Patients with a prostate volume greater than 80 g had HoLEP surgery, whereas those with a volume less than 80 g underwent TURP surgery. All cases were operated on by the same surgeon, who performs at least 100 HoLEP and TURP procedures each year. Each consecutive cohort consisted of 25 patients who met the study's inclusion criteria and gave consent to participate in the study.

We included patients with American Society of Anesthesiologists (ASA) scores of I–III who had BPH and were scheduled for HoLEP or TURP surgery under general anesthesia. Patients were excluded if they were diagnosed with an immune system disease, diabetes mellitus, non-prostate-related malignancies or for having a history of steroid use in the last 3 months.

Clinical variables consisting of age, body mass index, ASA score, operation duration, blood pressure, heart rate, body temperature, postoperative pain scores, and laboratory parameters were also assessed. Laboratory variables, including white blood cell (WBC) count, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), neutrophil-to-lymphocyte ratio (NLR), CD4+/CD8+ ratio, and adrenaline and cortisol levels were measured at three time points: before the operation (pre-OP), immediately after the operation (post-OP), and on postoperative day 1 (POD1).

Surgical Techniques

The equipment used for HoLEP was as follows: a high-power holmium laser (100- or 120-W platform, Lumenis, Yokneam, Israel); an end-firing 550-micron laser fiber with an energy setting of 2.0 J and frequency settings of 40–50 Hz; a continuous-flow 26F resectoscope with a distal bridge; a 7F catheter through the proximal bridge to stabilize the laser fiber; continuous saline irrigation; a rigid indirect nephroscope with a 5 mm working channel; a tissue morcellator; and a video system. The classical HoLEP technique was used as described previously (7). This method involves the 5 and 7 o'clock incisions and enucleation of one median and two lateral lobes.

TURP surgery was carried out using a cutting mode setting of 120 W, a coagulation mode setting of 100 W, a continuous-flow 26F resectoscope with a rotating inner tube, an active bipolar working element from Karl Storz, and loop electrodes (all Karl Storz, Germany). The irrigate used was isotonic 0.9% saline at room temperature. The operation technique for TURP was the Mauermayer method (8). In this method, resection starts with the middle lobe and continues with the resection at 9 and 3 o'clock.

Anesthesia Protocol

All patients received premedication with 2 mg of midazolam intravenously before induction of anesthesia. Induction was accomplished with propofol (1.0–2.0 mg/kg), fentanyl (2 mcg/kg), and rocuronium (0.6 mg/kg). Intubation was done using an endotracheal tube. Anesthesia was maintained with sevoflurane in a 1:1 mixture of nitrous oxide and oxygen. The end-tidal concentration of sevoflurane was maintained at 1–2%. Fentanyl boluses (25–50 μg intravenously) were administered as deemed necessary by the attending anesthesiologist. All patients were given tramadol (1 mg/kg) and paracetamol (15 mg/kg) as an intravenous infusion at the end of the operation. Neuromuscular blockade was reversed with neostigmine and atropine based on the train-of-four results.

Pain Score

All patients were asked to rate their current pain intensity by 1) making a vertical mark on a 10 cm visual analog scale (VAS) ranging from "no pain" on the left to "worst pain" on the right and 2) selecting a number between 0 and 10, where 0 was "no pain" and 10 was "worst pain."

Flow Cytometric Immunophenotyping

Whole blood samples were analyzed using flow cytometry to determine the T cells (CD3+), helper T cells (CD3+/CD4+), cytotoxic T cells (CD3+/CD8+), activated T cells (CD3+/HLA-DR+), B cells (CD19+), and NK cells (CD56+/CD16+/CD3-). Briefly, lymphocyte subsets were measured by multiple-color flow cytometry with human monoclonal anti-CD3-APC-A750 (Beckman Coulter, US), anti-CD4-APC (Beckman Coulter, US), anti-CD8-PC7 (Beckman Coulter, US), anti-CD56-APC-A700 (Beckman Coulter, US), anti-CD16-FITC (Beckman Coulter, US), anti-HLA-DR-PB (Beckman Coulter, US), and anti-CD19-ECD (Beckman Coulter, US) according to the manufacturer's instructions. Results were analyzed using the Kaluza software (Beckman Coulter).

Interleukin-6 and Tumor Necrosis Factor Alpha Measurement

Serum was separated by centrifugation as soon as blood was taken from the patients. Serum samples were stored at -20 degrees for no longer than 2 months. IL-6 and TNF-a levels were measured by enzyme-linked immunosorbent assay using the DIAsource IL-6-EASIA Kit (DIAsource Immunoassays S.A., Belgium) and the DIAsource TNF-a-EASIA Kit (DIAsource Immunoassays S.A., Belgium), respectively. The assay was performed according to the manufacturer's instructions. Standard and clinical samples were pipetted into the wells with an immobilized antibody specific for IL-6 and TNF-a. The wells were washed with an automatic microtiter plate washer (Combiwash, Human Diagnostics, Germany). As the last step, the wells were measured at 450 nm. The results were calculated by the means of standard curves. Based on the manufacturer's manual, the minimum detectable doses of IL-6 and TNF-a were assumed to be 2 pg/ml and 0.7 pg/ml, respectively, and samples were evaluated considering these criteria.

Statistical Analysis

The Shapiro–Wilk test was used to verify the normality of the distribution of continuous variables. Continuous variables are presented as mean ± SD or median (interquartile range), and categorical variables are presented as numbers. Comparisons between the groups were made using Fisher's exact test for categorical variables, the Mann–Whitney U test was used to compare the median values of two nonparametric variables, and the Student's t-test was used to compare the mean values of two independent parametric continuous variables. The Friedman test was used to compare the median values of IL-6 and TNF-a for intragroup comparisons. All statistical procedures were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL). A P value of < 0.05 was considered significant.

RESULTS

Demographic and clinical characteristics of the patients who underwent HoLEP or TURP surgery are presented in Table 1. One patient in the HoLEP group was excluded from the study because of his conversion to open prostatectomy due to bleeding. The mean age was 63.1 ± 6.7 years old. There was no significant difference between the groups in terms of age, body mass index, or ASA scores. However, the operation time was statistically shorter in the TURP group ($p = 0.001$). Body temperature at the end of the operation was statistically significantly lower in the HoLEP group ($p = 0.006$). HoLEP surgery was superior to TURP surgery in terms of postoperative pain and length of hospital stay. The VAS scores at the 4th and 24th hours postoperatively were statistically significantly lower in the HoLEP group ($p = 001$ and $p = 0.015$, respectively). The length of hospital stay was shorter in the HoLEP group ($p = 0.010$).

We examined the perioperative trends in WBC, CRP, IL-6, TNF-a, NLR, CD4+/CD8+ ratio, and adrenaline and cortisol levels in all patients who had a prostatectomy and compared the mean values of the markers at post-OP or POD1 with those at pre-OP. CRP and IL-6 were significantly higher at post-OP than at pre-OP ($p < 0.001$). IL-6 and CRP continued to be significantly higher at POD1 than at pre-OP ($p < 0.001$). The mean levels of TNF-a decreased at post-OP ($p < 0$ .001). There were no differences in the levels of TNF-a between pre-OP and POD1. WBC and NLR were significantly higher at POD1 then at pre-OP ($p < 0.001$ and $p = .001$, respectively). No differences were observed for the perioperative levels of the serum CD4+/CD8+ ratio or adrenaline and cortisol values.

The results of WBC, CRP, IL-6, TNF-a, NLR, and

Table 1. Patient demographics, operative data, and follow-up results

Variable	HoLEP (n = 24)	TURP (n = 25)	P value
Age (years)	65.4 ± 7.3	61.3 ± 5.7	0.111[a]
BMI	27.3 ± 1.5	26.8 ± 2.2	0.440[a]
ASA score (n)			
I	6	5	0.741[b]
II	13	12	0.777[b]
III	5	8	0.520[b]
Prostate volume (ml)	110.8 ± 18.8	57.8 ± 13.6	***0.001*** [a]
Preoperative heart rate (beat/minute)	69 ± 8	71 ± 11	0.633[a]
Preoperative systolic blood pressure (mm HG)	111 ± 18.6	108.2 ± 22.7	0.816 [a]
Operation duration (minutes)	135.4 ± 63.2	71.4 ± 23.2	***0.001*** [a]
Enucleation time (minutes)	103.2 ± 50.7	NA	NA
Morcellation time (minutes)	19.3 ± 9.1	NA	NA
Postoperative pain score			
Postoperative 4th hour	1.9 ± 1.5	4.9 ± 2	***0.001*** [a]
Postoperative 24th hour	2.5 ± 1.6	3.8 ± 1.4	***0.015*** [a]
Postoperative body temperature (Celsius)	35.8 ± 0.8	36.6 ± 0.4	***0.006*** [a]
Hospital stay (days)	1.5 ± 0.6	2.6 ± 0.6	***0.010*** [a]

BMI, body mass index; ASA, American Society of Anesthesiology; NA, Not Applicable.
*Data are presented as mean (SD) except where otherwise indicated.
[a] Student's t-test. [b] Fisher exact test. Significant values are in bold and italics.

CD4+/CD8+ measurements at three different time intervals according to the HoLEP and TURP groups are shown in Table 2. Among these values, CRP levels were found to be significantly higher in the TURP group at post-OP and POD1 ($p < 0.05$) (Figure 1). IL-6 was also significantly higher in the TURP group at POD1 ($p <0 .05$) (Figure 2). WBC and NLR increased more rapidly in the TURP group at post-OP and POD1, but these increases did not reach statistical significance when compared to the HoLEP group. There was no significant difference between the two groups in terms of the levels of the stress hormones adrenaline and cortisol at the three different time intervals.

DISCUSSION

This prospective non-randomized study evaluated perioperative changes in stress markers with clinical outcomes in a short postoperative period after TURP or HoLEP surgery. We found that CRP and IL-6 levels were significantly higher after TURP surgery compared to HoLEP surgery. Additionally, based on the surgical stress markers examined in this study, HoLEP surgery was suggested to be associated with less tissue damage than TURP surgery.

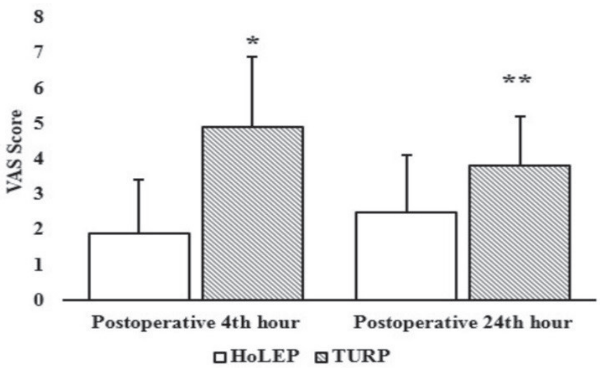
Surgical injury results in an acute-phase reaction. The acute-phase reaction initiates local and systemic responses to restore physiological homeostasis. The production of proinflammatory mediators and

Table 2. Changes in inflammatory markers

Markers	HOLEP (n = 24)	TUR-P (n = 25)	P value
WBC (10^9 /L)			
Pre-OP	6.3 ± 1.4	6.5 ± 1.1	0.703[a]
Post-OP	6.8 ± 1.4	7.4 ± 1.1	0.181[a]
POD1	9.8 ± 2.5	10.7 ± 2.9	0.096[a]
CRP (mg/L)			
Pre-OP	4.8 ± 2.6	3.5 ± 1.4	0.486[a]
Post-OP	12.6 ± 5.4	28.9 ± 7.8	***0.019***[a]
POD1	38 ± 10.8	70.5 ± 15.6	***0.013***[a]
IL-6 (pg/ml)			
Pre-OP †	21.2 (11.4–30.2)	15.6 (13.2–23.2)	0.315[b]
Post-OP †	55.9 (27.1–88.3)	57.5 (44.2–73.2)	0.379[b]
POD1 †	53.4 (40–124.1)	120 (92–154.5)	*0.**006***[b]
TNF-a (pg/mL)			
Pre-OP †	2.7 (2.3–3.3)	2.4 (2.1–3.1)	0.502[b]
Post-OP †	1.8 (0.9–2.3)	1.7 (1.2–2.5)	0.621[b]
POD1 †	2.3 (1.1–3.8)	2.5 (1.8–2.8)	0.903[b]
CD4+/CD8+ ratio			
Pre-OP	1.7 ± 0.7	1.8 ± 0.3	0.809[a]
Post-OP	1.5 ± 0.3	1.6 ± 0.5	0.854[a]
POD1	1.9 ± 0.6	1.9 ± 0.4	0.986[a]
Neutrophil-to-lymphocyte ratio			
Pre-OP	2.3 ± 1	2.1 ± 0.7	0.776[a]
Post-OP	2.1 ± 0.6	2.7 ± 0.6	0.174[a]
POD1	4.5 ± 2.2	5 ± 1.6	0.794[a]

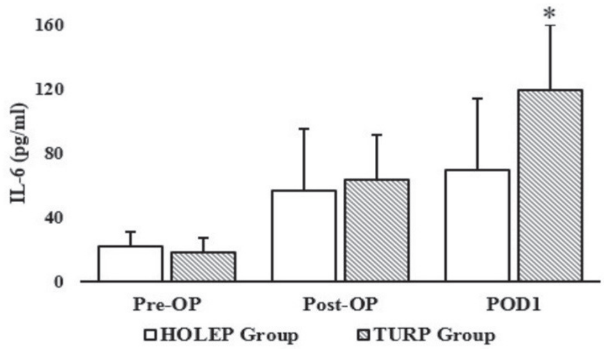
CRP, C-reactive protein; IL, interleukin; HoLEP, holmium laser enucleation of the prostate; NLR, Neutrophil-to-lymphocyte ratio; POD1, postoperative day 1; Post-OP, immediately postoperative; Pre-OP, preoperative; TURP, laser transurethral resection of the prostate;TN-F-a, tumor necrosis factor alfa; WBC, white blood cell.
*Data are presented as mean (SD) except where otherwise indicated.
† Data are presented as median (interquartile range).
[a] Student t-test [b] Mann-Whitney *U* test. Significant values are in bold and italics.

Figure 1. Comparison of postoperative pain scores between the groups



HoLEP, holmium laser enucleation of the prostate; VAS, visual analog scale; TURP, laser transurethral resection of the prostate. *P < 0 .05 compared at the 4th postoperative hour. **P < 0 .05 compared at the 24th postoperative hour.

Figure 2. Comparison of IL-6 levels between the groups



IL, interleukin; HoLEP, holmium laser enucleation of the prostate; POD1, postoperative day 1; Post-OP, immediately postoperative; Pre-OP, preoperative; TURP, laser transurethral resection of the prostate. *P < 0 .05 compared at postoperative day 1.

the activation of the humoral and cellular immune systems occur during this process (9). Local reactions occur at the site of surgical injury and result in endothelial cell production of cytokines. Cytokines such as interleukin-1, IL-6, and TNF-a are soluble indicators for both local and systemic inflammatory reactions as part of the acute-phase response (10,11). The systemic reaction includes activation of the plasma coagulation cascade, the release of complement, and the production of hepatic acute phase reactants such as CRP and α1-acid glycoprotein. IL-6 is the major regulator of the cytokine-mediated response and CRP is the most sensitive acute-phase reactant initiated by surgical injuries. IL-6 and CRP levels have been used as an objective biochemical marker to reflect the degree of operative injury (10). Many studies have shown a lower IL-6 response after minimally invasive surgery than after open surgery (10,12,13). In addition, Shintaro et al. reported a lower IL-6 response after laparoscopic radical prostatectomy than after open radical prostatectomy (14). In our study, compared with the preoperative values, IL-6 increased by almost three times in both groups immediately after surgery. Furthermore, IL-6 and CRP levels were significantly higher in the TURP group than in the HoLEP group at POD1. These findings support there being higher surgical injury with TURP compared to HoLEP.

The improved hemostasis provided by the HoLEP surgical technique, as well as the reduced depth of penetration into the prostate tissue, may be the mechanism responsible for the lower rise in inflammation markers observed in the HoLEP group compared to the TURP group in our study. Micheal et al. reported that the mean depth of thermal injury caused by bipolar TURP was 2.4 mm in their study of 12 patients with BPH treated surgically (15). However, the penetration depth of HoLEP in prostatic tissue is only 0.4 mm. HoLEP technology generates a pulsed solid-state laser with a wavelength of 2140 nm. This laser's wavelength is substantially absorbed by water, making it more suitable for use in an aquatic environment (16). Furthermore, it has been suggested that HoLEP may become the standard for surgical management of BPH, especially in patients on anticoagulants and bleeding diathesis (17).

In this study, the surgery duration of HoLEP was longer than that of TURP despite the fact that HoLEP showed advantages over TURP in terms of pain score and hospital stay during the perioperative phase. A previous study showed the difference in surgical duration between TURP and HoLEP (17). It is generally thought that HoLEP needs a longer operative time than TURP due to a greater resection ratio of prostate tissue with HoLEP. Past studies showed that HoLEP resects much more prostate tissue than TURP, as demonstrated by a larger drop in postoperative serum prostate-specific antigen levels, and that when the surgical time was corrected for tissue removed, HoLEP was similarly effective (18,19). In our study, the HoLEP group had a greater prostate size; the extra time needed for morcellation of the enucleated tissues may be responsible for the longer operation time with HoLEP.

Intraoperative hypothermia is common, with an incidence of around 60%. Cold bladder irrigation fluid is a significant source of heat loss during TURP, resulting in intraoperative hypothermia of 1–2° C (20). The elderly are a significant risk category because of the physiological changes associated with aging, which contribute to a decreased ability for thermoregulation. Reduced norepinephrine release and a-adrenoreceptor downregulation adversely impact the vasomotor response to cold in the elderly (20,21). Additionally, as lean body mass declines with age, shivering and thus metabolic heat generation tend to decrease. Hypothermia can have serious effects, including decreased blood flow to all systems, cardiac arrhythmias, a 400% to 500% increase in tissue oxygen demand, decreased metabolism, impaired platelet function, and increased susceptibility to surgical wound infection (21). In this study, body temperature, pulse, oxygen saturation, and blood pressure were monitored as standard care during anesthesia. We found that postoperative body temperature was significantly lower in the HoLEP group compared to the TURP group. This may be because HoLEP surgery lasted longer and possibly needed more irrigation fluid. We used all fluids at room temperature, similar to our routine clinical practice. It has been suggested that warming irrigation fluids may reduce the risk of hypothermia. However, warming large volumes of irrigation fluid may not always be practical. For this reason, the use of forced warm air has been recommended in long-term surgeries or especially in groups more sensitive to hypothermia to prevent adverse events.

There are also several limitations to this study. The patients were allocated to each group depending on prostate size. However, this nonrandomized study included having statistically similar cohorts in terms of the patients' age, weight, and ASA scores. The HoLEP group comprised the patients with a larger prostate volume. Considering the long resection time in the HoLEP group, it is likely that more prostate volume resections were performed. However, the volume of the resected tissue or postoperative PSA measurements were not obtained to confirm this.

In conclusion, both HoLEP and TURP surgery cause an increase in CRP and IL-6, which are indicators of surgical injury. These increases in surgical responses were less pronounced in HoLEP surgery compared to TURP surgery.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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