

Research article/Raziskovalni prispevek

LAPAROSCOPIC RADICAL PROSTATECTOMY DOES NOT CAUSE SIGNIFICANT TISSUE ISCHEMIA

LAPAROSKOPSKA RADIKALNA PROSTATEKTOMIJA NE POVZROČA POMEMBNE ISHEMIČNE OKVARE

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Key words *prostatic carcinoma; laparoscopic radical prostatectomy; classic retropubic radical prostatectomy; pressure of CO₂; tissue ischemia; glutathione peroxidase; superoxide dismutase; catalase; morphometry*

Abstract

Background *Today, laparoscopic radical prostatectomy is a commonly used operation with patients suffering from prostatic carcinoma. In contrast to the classic open radical prostatectomy, the laparoscopic approach is more patient-friendly, whereas long-term results are similar with both methods. CO₂ which is being insufflated during laparoscopic radical prostatectomy at a pressure of 12–14 mm Hg, could cause ischemic disorder of tissue in operating field.*

Patients and methods *The research group consisted of 44 patients with prostatic carcinoma, coming from the Department of Urology of General Hospital Slovenj Gradec; they were treated with laparoscopic radical prostatectomy, namely the Montsouris technique. The control group however, consisted of 11 patients with prostatic carcinoma from the Department of Urology of the Maribor Teaching Hospital. They were treated with a classic retropubic radical prostatectomy. Besides clinical data and pathological examinations, patients from both groups were examined for activity of GSH-Px, SOD and CAT enzymes in the venous blood before the operation and immediately after it. After the operation we also took a tissue sample of each patient's bladder neck for immune histochemical and morphometrical examination of open capillary surface.*

Results *Patients of both groups were clinically comparable. Those, treated with the laparoscopic method had longer operating time than patients treated with the classic approach (219:140 min.), there was also a lower blood loss (343:542), shorter analgesic therapy (3.2:6.5 days), shorter period of urinary catheterisation (5.3:14.7 days). Patients treated laparoscopically, had no statistically notable change in the activity of GSH-Px, SOD and CAT enzymes in the venous blood after the operation in comparison to the activity before the operation. There was also no statistically notable difference in open capillary surface on bladder neck exterior among patients of research and control group.*

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Conclusions *The activity of GSH-Px, SOD and CAT enzymes in the venous blood and the morphometrical analysis of capillary surface on bladder neck exterior show that 12-14 mm Hg pressure of CO₂ during the laparoscopic transabdominal radical prostatectomy does not damage microcirculation.*

Ključne besede *karcinom prostate; laparoskopska radikalna prostatektomija; klasična retropubična radikalna prostatektomija; tlak CO₂; ishemija tkiva; glutation peroksidaza; superoksid dismutaza; katalaza; morfometrija*

Izveček

Izhodišča *Karcinom prostate je v razvitem svetu najpogostejša maligna bolezen pri moških, starejših od 50 let. Laparoskopska radikalna prostatektomija je danes pogosto uporabljana operacija pri bolnikih s karcinomom prostate. Za razliko od klasične odprte radikalne prostatektomije je laparoskopski pristop za bolnika prijaznejši, dolgoročni izidi pa podobni pri obeh metodah. Plin CO₂, ki ga insufliramo med laparoskopsko radikalno prostatektomijo, s tlakom med 12 in 14 mm Hg, bi lahko povzročal ishemične okvare na tkivih v operacijskem področju.*

Bolniki in metode *V prospektivni primerjalni klinični raziskavi smo oblikovali dve skupini bolnikov. V preiskovano skupino je bilo vključenih 44 bolnikov s karcinomom prostate iz Urološkega oddelka Splošne bolnišnice Slovenj Gradec; zdravili smo jih z laparoskopsko radikalno prostatektomijo s tehniko Montsouris. V kontrolno skupino pa je bilo vključenih 11 bolnikov s karcinomom prostate iz Urološkega oddelka Učne bolnišnice Maribor. Ti so bili zdravljeni s klasično retropubično radikalno prostatektomijo. Poleg kliničnih podatkov in patoloških preiskav smo bolnikom v obeh skupinah določali aktivnost encimov GSH-Px, SOD in CAT v venski krvi pred začetkom operacije in neposredno po njej. Prav tako smo vsem bolnikom na koncu operacije vzeli košček tkiva s površine vratu sečnika za imunohistokemično in morfometrično preiskavo površine odprtih kapilar.*

Rezultati *Bolniki preiskovane in kontrolne skupine so si bili med seboj klinično primerljivi. Pri tistih, ki so bili operirani po laparoskopski metodi, je operacija trajala dalj časa (219 ± 43 min.) kot pri klasično operiranih (140 ± 13 min.). Količina izgubljene krvi med operacijo je bila signifikantno manjša pri laparoskopsko operiranih bolnikih (343 ± 265 ml) v primerjavi z bolniki v kontrolni skupini (542 ± 157 ml). Analgetična terapija je trajala pomembno krajši čas pri bolnikih v preiskovani skupini ($3,2 \pm 1,1$ dneva) kot pri bolnikih v kontrolni skupini ($6,5 \pm 2,1$ dneva). Laparoskopsko operirani bolniki so nosili urinski kateter bistveno krajši čas ($5,3 \pm 1$ dan) v primerjavi s klasično operiranimi bolniki ($14,7 \pm 6,2$ dneva). Aktivnost encimov GSH-Px, SOD in CAT v venski krvi ni bila statistično pomembno spremenjena na koncu operacije v primerjavi s tisto, na začetku med laparoskopsko operiranimi bolniki. Površina odprtih kapilar na zunanji površini vratu sečnega mehurja ni bila statistično pomembno različna med bolniki preiskovane in kontrolne skupine.*

Zaključki *Laparoskopska radikalna prostatektomija traja dalj časa kot klasična operacija, a je pri laparoskopskem pristopu manjša izguba krvi, krajša analgetična terapija in krajše nošenje uretralnega katetra. Aktivnost GSH-Px, SOD in CAT encimov v venski krvi in morfometrična analiza površine kapilar na zunanji površini vratu sečnega mehurja kažeta, da tlak CO₂ med 12–14 mm Hg med laparoskopsko transabdominalno radikalno prostatektomijo ne povzroča okvare na mikrocirkulaciji.*

Introduction

Prostate cancer is the most common malignant disease of the modern world affecting men over 50 years of age. Incidence is between 2 and 137/100,000 men. The occurrence growth is factual or apparent, also because of better diagnostics and population ageing (1). The first radical perineal prostatectomy was performed by Young in 1904 (2). In the past there were many complications with patients treated by the clas-

sic method, especially intraoperative bleeding, incontinence and impotence. According to Walsh's research, the occurrence of complications has significantly diminished (3).

The history of laparoscopy began more than 100 years ago. Kelling (4) described the celioscopy technique in 1901. Crucial for further development of laparoscopic surgery was insufflation of CO₂ to the abdominal cavity, introduced by Zollkofer in 1924 (5). During today's laparoscopic operational proce-

dures in the abdominal cavity and retroperitoneal area, CO₂ is routinely insufflated at a pressure of 12–15 mm Hg (6).

In comparison to the standard retropubic radical prostatectomy, the laparoscopic radical prostatectomy is, when treating prostate cancer, more patient-friendly, better at preserving functions and its oncological results are fully comparable to the ones of an open surgery (6–10). Some operation techniques and approaches have won recognition, for example Guillonnet al. (6) – Montsouris technique. Rassweiler (11) uses an ascending so-called Heilbronn technique. The method is to a certain extent similar to the standard retropubic radical prostatectomy. Menon et al. (12) of the Vattikuti Institute in Detroit introduced the robotic radical prostatectomy technique.

The Department of Urology of General Hospital Slovenj Gradec (GH SG) performed the first laparoscopic radical prostatectomy in 1999 (13) using a transperitoneal approach and the Montsouris operating technique. By the end of June 2006 we performed 383 operations. Complications during and after such procedures have been studied ever since the introduction of laparoscopic operations. In one of the largest series of patients treated with the laparoscopic technique, there were 17.1 % of complications among 567 patients (14). What was also studied was physiological changes, especially changes in splanchnic circulation using different laparoscopic approaches.

Laparoscopic radical prostatectomy takes approximately 3 hours or sometimes more. There was never a clear answer to whether the pressure of insufflated CO₂ in the operative area damages the microcirculation and causes temporary or permanent ischemic disorder. Reflow after the ischemic disturbance can also be dangerous. As early as 1954 Gerschman determined the toxicity of oxygen radicals, which generate to a greater extent after the cessation of ischemia. Possible ischemic disorder of organ surface in the abdominal cavity during the operation was to be established by increasing the activity of those enzymes in the systemic circulation, which generate during tissue ischemia. The reason for notable ischemia of bladder surface itself was to be established by means of morphometrical capillary analysis.

The prospective comparative study was to show whether increased CO₂ pressure in the abdominal cavity causes notable reduction of splanchnic capillary circulation. This would be seen in increased activity of enzymes, generated during ischemia, and in reduced capillary surface of the bladder exterior. In this case we would expect a significant difference between laparoscopically treated patients and patients, treated in line with the standard retropubic method.

Patients and methods

Patients included in the research suffered from localized prostate cancer (established by prostate needle biopsy), were younger than 70 years and their PSA value was lower than 20 ng/ml and the Gleason score lower than 7.

The research group consisted of patients from the GH SG. They were treated with the laparoscopic method (Montsouris technique and 12–14 mm Hg pressure of CO₂). The control group consisted of patients from the Department of Urology of the Maribor Teaching Hospital (TH MB). They were treated according to the standard retropubic radical prostatectomy method (13).

Before the operation all patients underwent a transrectal ultrasound to determine prostatic size and volume.

We measured every patient's procedure duration, quantity of blood loss, duration of analgesic therapy, in-bed time, duration of urinary catheterisation, hospitalisation time and the frequency of incontinence and impotence after the operation.

We took a sample of every patient's venous blood to determine the activity of GSH-Px, SOD and CAT (15–18) enzymes. The blood was centrifuged and plasma, frozen to –18 °C, was sent to the Clinical Institute of Clinical Chemistry and Biochemistry, Ljubljana University Medical Centre. When preparing the bladder, a sample of tissue from the entire patient's bladder wall was taken. Fixed tissue was then sent to the Institute of Pathology of the Faculty of Medicine in Ljubljana, where a pathohistological examination, an immune histochemical and a morphometrical examination of capillary surface were made. The immune histochemical examination was made by means of endothelial cell marker CD31. Antigen was demonstrated with the MSAPE method (Microwave Strept-Avidin Peroxidase Enzyme). That is how it became visible under the microscope.

After the prostate and its seminal vesicles had been removed, the sample was weighted. Pathohistological examination determined the differentiation of the tumour, its expansion in the gland and possible infiltration of malignant cells in the surgical margin.

Morphometrical examinations helped us to determine open capillary surface of external bladder wall. Every sample held 10 observed fields at 20× magnification. Statistical analysis was made by means of calculating descriptive data and also by employing test t, paired t-test and chi-square test.

Clinical research was approved by the National Medical Ethics Committee of the Republic of Slovenia on May 14, 2002.

Results

Between June 1, 2002 and March 31, 2003, the GH SG treated 44 patients suffering from localized prostate cancer with the laparoscopic method. In the same time the TH MB treated 11 patients (control group) suffering from the same disease with the standard retropubic approach. The main clinical and some laboratory data are seen in Table 1.

The patients' average age was 62.6 ± 11.3 (SD) years in the research group and 61.8 ± 9.9 (SD) years in the control group. Age difference was statistically insignificant.

Patients' body weight was 80.5 ± 10.6 (SD) kg in the research group and 79.2 ± 8.9 (SD) kg in the control

group. Difference in weight was statistically insignificant.

Table 1. *Division of patients into the research group (GH SG, laparoscopic prostatectomy) and the control group (TH MB, retropubic prostatectomy), PSA value, Gleason score, operation and hospitalisation process (average \pm STD).*

Razpr. 1. *Porazdelitev bolnikov na preiskovano skupino (GH SG, laparoskopska prostatektomija) in kontrolno skupino (TH MB, retropubična prostatektomija), vrednost PSA, Gleasonovega indeksa, potek operacije in hospitalizacije (povprečje \pm STD).*

	Research group Preiskovana skupina	Control group Kontrolna skupina	Significance level Statistična signifikantnost
Patient-number (%) Bolniki-število (%)	44 (80)	11 (20)	
PSA (ng/ml) PSA (ng/ml)	6.5 \pm 3.6	7.1 \pm 3.3	0.640
Gleason score before operation Gleasonov indeks pred operacijo	5.7 \pm 0.9	6.1 \pm 3.2	0.021
Operating time (min.) Trajanje operacije (min.)	219 \pm 43	140 \pm 13	0.000
Lost blood during operation (ml) Količina izgubljene krvi med operacijo (ml)	343 \pm 365	542 \pm 157	0.009
Prostate weight (g) Teža prostate (g)	40 \pm 11	43 \pm 8	0.220
Analgesic therapy duration (days) Trajanje analgetične terapije (dnevi)	3.2 \pm 1.1	6.5 \pm 2.1	0.000
Getting up (day) Vstajanje iz postelje (dan)	2.0 \pm 0.2	2.3 \pm 0.5	0.086
Catheterisation (days) Nošenje uretralnega katetra (dnevi)	5.3 \pm 1	14.7 \pm 6.2	0.001
Hospitalisation time (days) Trajanje hospitalizacije (dnevi)	9.1 \pm 2.5	10.8 \pm 4.3	0.235

Table 2 shows carcinoma expansion in the prostate, which was determined in a pathohistological examination of the removed gland, and the positive surgical margin of patients from the research group. Positive surgical margin was found in 25 % of patients.

Table 2. *Carcinoma expansion in the prostate of patients from the research group.*

Razpr. 2. *Razširjenost karcinoma v prostati pri bolnikih v preiskovani skupini.*

Pathological stadium Patološki stadij	Number of patients Število bolnikov	Positive surgical margin Pozitivni kirurški rob
pT2a/NO	11	0
pT2b/NO	11	2
pT2c/NO	18	6
pT3a/NO	4	3

NO = no metastases in the lymphatic glands
NO = brez zasevkov v bezgavkah

Figure 1 shows the activity of glutathione peroxidase in the venous blood of patients from research and control group before and after the operation.

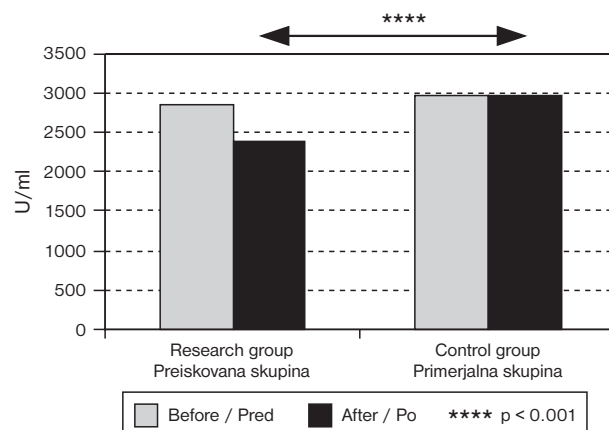


Figure 1. *Activity of glutathione peroxidase in the venous blood before and after the operation.*

Sl. 1. *Aktivnost glutatation peroksidaze v venski krvi pred operacijo in po njej.*

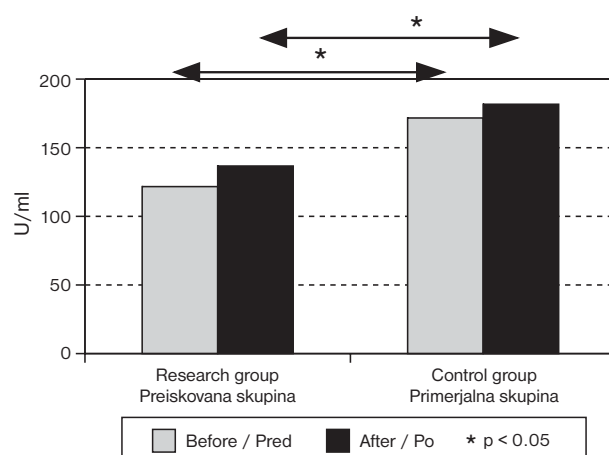


Figure 2. *Activity of superoxide dismutase in the venous blood before and after the operation.*

Sl. 2. *Aktivnost superoksid dismutaze v venski krvi pred operacijo in po njej.*

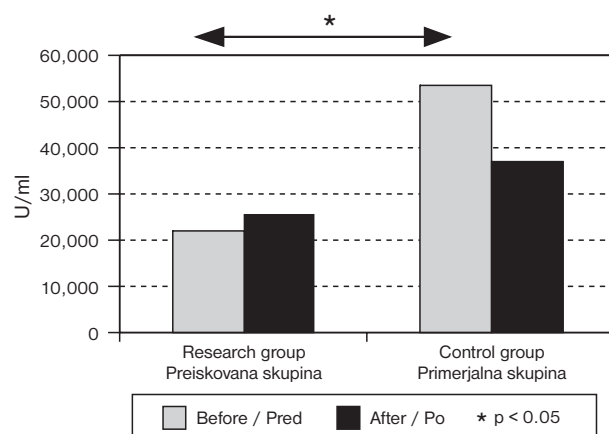


Figure 3. *Activity of catalase in the venous blood before and after the operation.*

Sl. 3. *Aktivnost katalaze v venski krvi pred operacijo in po njej.*

Figure 2 shows the activity of superoxide dismutase in the venous blood of patients from research and control group before and after the operation. Figure 3 shows the activity of catalase in the venous blood of patients from research and control group before and after the operation. Figure 4 shows the morphometrical analysis of open capillary surface on the external bladder wall in patients of both groups at the end of the operation.

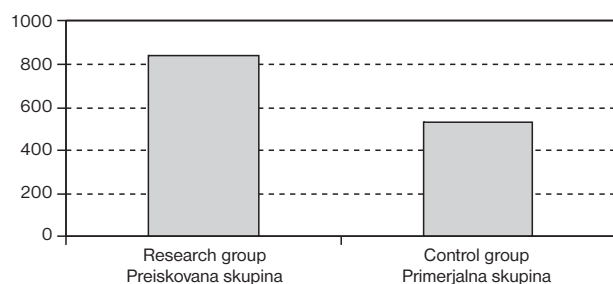


Figure 4. Morphometrical analysis (in μm^2) of open capillary surface on the external bladder wall in patients of both research and control group at the end of the operation.

Sl. 4. Morfometrična analiza (v μm^2) površine odprtih kapilar na zunanji površini vratu sečnega mehurja na koncu operacije v preiskovani in kontrolni skupini.

Figure 5 shows the frequency of incontinence in patients of both groups 3 weeks and 3 months after the operation.

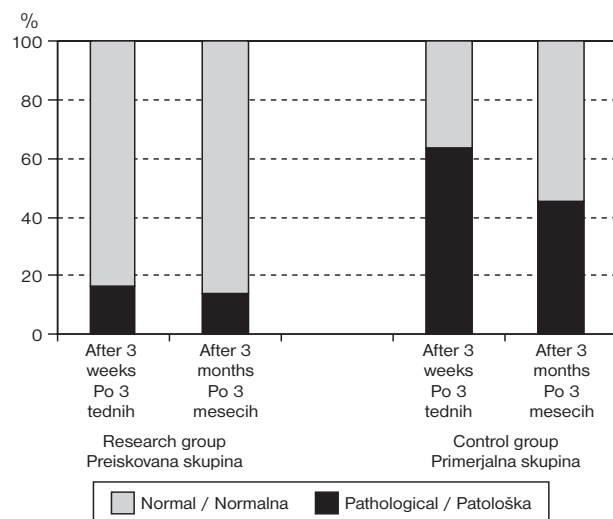


Figure 5. Frequency of incontinence in patients of the research group 3 weeks and 3 months after the operation.

Sl. 5. Pogostost inkontinence pri bolnikih v preiskovani skupini tri tedne in tri mesece po operaciji.

Impotence was present in 89 % of patients in research group and in 100 % of patients in control group 6 months after the operation.

Discussion

Laparoscopic radical prostatectomy due to prostate cancer is in contrast to the standard open operation more patient-friendly and has same oncological results. Patients treated laparoscopically must have healthier heart and lungs than patients treated with the classic method, because of long-lasting downwards upper body position during operation (19).

Patients from the research group had a similar PSA activity and prostate weight as those from the control group, whereas the Gleason score was notably higher, although clinically insignificant in the control group. The operation time was significantly longer with patients from the research group. Patients of the research group had considerably lower blood loss during operation, shorter analgesic therapy and shorter urinary catheterisation periods. Patients of the research group also had shorter in-bed time than the patients of the control group, though the difference was statistically insignificant. Hospitalisation time was comparable at both groups. The results obtained are congruent with those of Eden and Moon (20). Thus, our results are comparable with theirs regarding the pathological classification of tumour expansion in the prostate.

Three weeks and also three months after the operation, urinary incontinence was statistically notable more uncommon in patients of the research group than in those of the control group.

Many researchers have studied the entire splanchnic circulation and the microcirculation during laparoscopic procedures. Schelling et al. (21) measured microcirculation in the splanchnic area during laparoscopic cholecistectomy. They established diminished blood flow by 40–54 % to the stomach, by 32 % to the jejunum, by 44 % to the colon, by 39 % to the liver and by 60 % to the parietal peritoneum. Eleftheriadis et al. (22) used a special laser to measure microcirculation in the liver and pH of stomach during laparoscopic cholecistectomy. They established reduced circulation in the liver and pH increase in the gastric mucosa but the condition returned to normal rapidly after CO_2 was separated from the peritoneal cavity. Odeberg et al. (23) on the other hand could not confirm this. What they established was increased concentration of catecholamines in the plasma, irrespective of the patient's position during the operation.

In case ischemia is prolonged, it is followed by capillary endothelium oedema, hemoconcentration, trombocyte and leukocyte adhesion followed by nearby oedema. This phenomenon is well known in experimental circumstances in myocardial infarction and striated muscles, though it is the same in all organs and tissues (25–28).

Cu/Zn superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) are three primary enzymes protecting the cell from free oxygen radicals during reoxygenation after ischemia (29). At mild ischemic disorder their activity is increased and at serious one, their activity is first strongly increased and later strongly decreased.

The activity of enzymes, glutathione peroxidase, superoxide dismutase and catalase remained unchanged during operation in patients of research group. This excludes significant tissue ischemia, at least such that would reflect in a changed activity of enzymes in systemic circulation. Surprisingly, even catalase activity before the operation was significantly higher at patients of the control group than at those of the research group. The same goes for glutathione peroxidase activity after the operation and superoxide dismutase activity both, before and after operation. The morphometrical analysis of open capillary surface on bladder neck after the operation shows that there is no significant difference between patients of both groups, although capillary surface was greater in the research group. CO₂ itself causes dilation of capillary. In case of serious ischemic disorder, first arteriole or precapillary sphincters' constriction would occur and later also dilatation and even bleeding or thrombosis may happen. It is estimated that morphometrical analysis of tissue, which was exposed to CO₂ at the pressure of approximately 13 mm Hg, showed no significant ischemic disorder.

Conclusions

Before surgical treatment the research and the control group of patients were comparable to each other. Laparoscopic radical prostatectomy was more patient-friendly than the classic retropubic prostatectomy. The activity of GSH-Px, SOD and CAT enzymes in the venous blood after the operation proves that there were no systemic signs for tissue ischemia. Pathohistological examination and the morphometrical analysis of the bladder neck surface tissue show that there were also no signs for ischemic disorder caused by insufflation of CO₂ during laparoscopic radical prostatectomy.

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