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Lithuanian clinical trial of treatment of hemorrhoids

Double-blind randomized controlled trial comparing laser hemorrhoidoplasty with sutured mucopexy and excisional hemorrhoidectomy

SUMMARY OF DOCTORAL DISSERTATION

Medicine and health sciences,
Medicine (M 001)

VILNIUS 2020

This doctoral dissertation was prepared at the Clinic of Gastroenterology, Nephrourology, and Surgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, in 2015–2019.

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This doctoral dissertation will be defended in a public meeting of the Dissertation Defence Panel:

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The dissertation will be defended at a public meeting of the Dissertation Defence Panel at 14:00 hour on 29th May 2020 in the Fifth audience of Vilnius University Hospital Santaros Klinikos.
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The dissertation is available at the library of Vilnius University and on the website: *www.vu.lt/lt/naujienos/ivykiu-kalendorius*

VILNIAUS UNIVERSITETAS

Donatas
DANYS

Lietuviškasis hemorojaus gydymo klinikinis tyrimas

Atsitiktinės atrankos lyginamasis hemoroidektomijos, hemorojaus kojytės perrišimo ir intrahemorojinės lazerinės operacijos tyrimas

DAKTARO DISERTACIJOS SANTRAUKA

Medicinos ir sveikatos mokslai,
Medicina (M 001)

VILNIUS 2020

Disertacija rengta 2015–2019 Vilniaus universitete.

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Disertacija bus ginama viešame Gynimo tarybos posėdyje 2020 m. gegužės 29 d. 14:00 val. Vilniaus universiteto ligoninės Santaros klinikų penktojoje auditorijoje.
Adresas: Santariškių g. 2, Vilnius, Lietuva.

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Abbreviations

LHP – laser hemorrhoidoplasty
HAL – hemorrhoidal artery ligation
EH – excision hemorrhoidectomy
J – joule
mm – millimeter
W – watt
SH – Stapled hemorrhoidopexy (PPH)
RBL – Rubber band ligation
ESCP – European Association of Coloproctology
IRC – Infrared Coagulation
USA – United States of America
SCL – sclerotherapy
VAS – visual analog scale
NAID – *Nonsteroidal* Anti-Inflammatory Drug
MHz – millihertz
HeLP – Hemorrhoidal Laser Procedure
RCT – Randomised Controlled trial
Etc. – et cetera
THD – Doppler-guided transanal hemorrhoidal dearterialization
nm – nanometre

Introduction

The research and debates on the best choice of treatment for hemorrhoids are on-going. The most effective procedure - excisional hemorrhoidectomy — causes the most pain to the patient [1]. Two recent large randomized trials compared excisional hemorrhoidectomy with stapled hemorrhoidopexy [2], and rubber band ligation with hemorrhoidal artery ligation [3]. The first trial conclusively proved that excisional hemorrhoidectomy is more effective and cheaper than stapled hemorrhoidopexy. The second trial showed rubber band ligation was shown to be as effective as Doppler-guided hemorrhoidal artery ligation after finishing the series of banding procedures. It is also significantly cheaper. However, significant and prolonged postoperative pain after excisional hemorrhoidectomy and high recurrence rate after rubber band ligation demand further improvement of treatment modalities of hemorrhoids.

Intrahemorrhoidal laser coagulation or laser hemorrhoidoplasty (LHP) was first described in 2009 [4] and reported in larger series of patients in 2010 [5]. A few case series, including our own experience [6], as well as the experience of Weyand [7], suggested this method to be a technically simple, minimally invasive, safe, and effective procedure for symptomatic hemorrhoids.

Doppler-guided hemorrhoidal artery ligation was compared with sutured hemorrhoidopexy, or mucopexy, alone in three randomized controlled trials [8,9,10], with all the trials showing no benefit of the Doppler use in controlling hemorrhoidal symptoms. Sutured hemorrhoidopexy without the use of Doppler (sometimes called sutured mucopexy) could be an inexpensive, minimally invasive alternative treatment for hemorrhoids.

Aim of the study

The aim of this study is to compare three different modalities for the treatment of symptomatic 2nd to 3rd degree hemorrhoids: open hemorrhoidectomy, intrahemorrhoidal laser procedure, and

hemorrhoidal pedicle ligation, also to optimize the method of laser hemorrhoidoplasty operation based on experimental and clinical data.

Tasks of the study

1. Evaluate distant results after laser hemorrhoidoplasty.
2. Evaluate coagulation depth during laser hemorrhoidoplasty in the experimental settings
3. Evaluate the effectiveness and the safety of LHP, compare the healing of patients after LHP and other surgical procedures.

Statements to be defended

1. Technical aspects, that provide best outcomes for the patients, are: sparing of perianal skin – avoid excision and coagulation; limited use of a maximum of 200-300 J of energy for each hemorrhoidal quadrant; circumferential perianal submucosal coagulation; no necessity of pedicle suture or ligation.
2. The laser beam of 1470 nm wavelength 8 watts 3 seconds coagulate perianal tissue diameter of 4 mm. The next area of coagulation should be placed 5 mm away from the previous beam.
3. LHP is less effective than EH and more effective than HAL. LHP is less painful and creates less discomfort for the patients than EH.

Practical and scientific significance

Intrahemorrhoidal laser coagulation or laser hemorrhoidoplasty (LHP) was first described in 2009 [4]. Further reports on larger series of patients [5] suggested this method to be a technically simple, minimally invasive, safe and effective procedure for symptomatic hemorrhoids. There are multiple technical variations used by different surgeons. The entry points, the use of apical sutures, the levels of energy used and the area of coagulation are all differently described

by different authors. We present the standardized technique which we routinely perform in our experience and which has well described medium-term outcomes.

The presentation and approbation of the results

Publications:

1. Poskus, T., Danys, D., Makunaite, G. et al. Results of the double-blind randomized controlled trial comparing laser hemorrhoidoplasty with sutured mucopexy and excisional hemorrhoidectomy. Int J Colorectal Dis 35, 481–490 (2020), from DOI:10.1007/s00384-019-03460-6
2. Danys, D., Pacevicius, J., Makunaite, G., et al. (2020). Tissue coagulation in laser hemorrhoidoplasty – an experimental study. Open Medicine, 15(1), pp. 185-189. Retrieved 20 Mar. 2020, from doi:10.1515/med-2020-0027

Presentations:

1. 2017 06 10 – 2017 06 14 American Society of Colon & Rectal Surgeons Annual Scientific Meeting, Tripartite Meeting, Seattle (USA):
   „Early and One-Year Results of Laser Haemorrhoidoplasty for Symptomatic Haemorrhoids“
   Authors: D. Danys, P. Mazrimas, E. Grisin, N. Zaks, S. Mikalauskas, D. Narmontas, K. Strupas, T. Poskus
2. 2018 04 16 – 2018 04 18 15th International Coloproctology Meeting. Turin (Italy)
   „Initial results of the randomized, double-blind clinical trial of laser hemorrhoidoplasty versus rectoanal repair versus open hemorrhoidectomy“
   Authors: D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas, T. Poskus.
   „Evaluation of medical laser effect on soft tissues during hemorrhoidectomy“

Authors: D. Danys, J. Pacevicius, G. Makunaite, R. Palubeckas, A. Mainelis, N. Markevicius, A. Rimkevicius, K. Strupas, T. Poskus.
Emborrhoid: method of choice for high risk patients with chronic hemorrhoids bleeding
Authors: N. Pranskeviciute, A. Sarskute; N. Zaks; D. Danys; T. Poskus.

3. 2018 05 10 – 2018 05 12 9th Congress of Baltic Association of Surgeons, Klaipeda (Lithuania)
„Evaluation of medical laser effect on soft tissues during hemorrhoidectomy“
Authors: J. Pacevicius, D. Danys, G. Makunaite, R. Palubeckas, A. Mainelis, N. Markevicius, A. Rimkevicius, K. Strupas, T. Poskus
„Initial results of the randomized, double-blind clinical trial of laser hemorrhoidoplasty versus rectoanal repair versus open hemorrhoidectomy“
Authors: D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, A. Dulskas, K. Strupas, T. Poskus.

4. 2018 05 24 IX Baltic-Belarusian Conference, VIII Belarusian Coloproctology Conference Polock (Belarus)
„Initial results of the randomized, double-blind clinical trial of laser hemorrhoidoplasty versus rectoanal repair versus open hemorrhoidectomy“
Authors: D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, A. Dulskas, K. Strupas, T. Poskus.
„Evaluation of medical laser effect on soft tissues during hemorrhoidectomy“.
Authors: D. Danys, J. Pacevicius, G. Makunaite, R. Palubeckas, A. Mainelis, N. Markevicius, A. Rimkevicius, K. Strupas, T. Poskus

5. 2018 08 29 – 2018 09 01 The 29th ISUCRS Biennial Congress, London (England)
„Initial results of the randomized, double-blind clinical trial of laser hemorrhoidoplasty versus rectoanal repair versus open hemorrhoidectomy“

Authors: D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas, T. Poskus.

„ Experimental Study of 1470-nm Diode Laser Hemorrhoidoplasty in Porcine Model“

Authors: D. Danys, J. Pacevicius, G. Makunaite, R. Palubeckas, A. Mainelis, N. Markevicius, A. Rimkevicius, K. Strupas, T. Poskus.

6. 2018 09 13 – 2018 09 16 South African Associate Endoscopic Surgeons (SASES), Cape Town (South Africa)

   „Initial results of the randomized, double-blind clinical trial of laser hemorrhoidoplasty versus rectoanal repair versus open hemorrhoidectomy“

   Authors: D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas, T. Poskus.

7. 2018 09 26 – 2018 09 28 (ESCP) 13th Scientific and Annual meeting European coloproctology association, Nica (France)

   „Initial results of the randomized, double-blind clinical trial of laser hemorrhoidoplasty versus rectoanal repair versus open hemorrhoidectomy“

   Authors: D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas, T. Poskus.

   „Experimental Study of 1470-nm Diode Laser Hemorrhoidoplasty in Porcine Model“.

   Authors: D. Danys, J. Pacevicius, G. Makunaite, R. Palubeckas, A. Mainelis, N. Markevicius, A. Rimkevicius, K. Strupas, T. Poskus.

8. 2018 11 06 – 2018 11 07 International Colorectal research congress. Seul (South Korea)

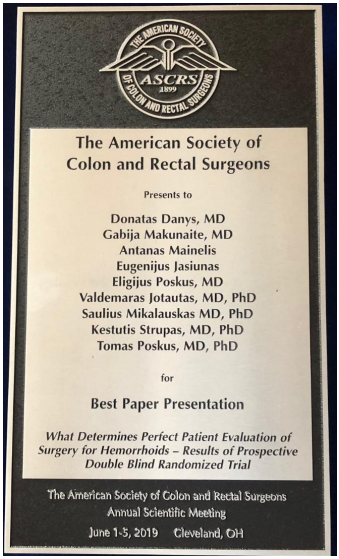
   „Initial results of the randomized, double-blind clinical trial of laser hemorrhoidoplasty versus rectoanal repair versus open hemorrhoidectomy“

   Authors: T. Poskus, D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas.

9. 2019 04 25 – 2019 04 26 Shiraz University of Medical Sciences congress „Benign Anorectal Diseases“, Shiraz (Iran)

„Randomized double-blind controlled trial of laser hemorrhoidoplasty, excisional hemorrhoidectomy and recto-anal repair for symptomatic haemorrhoids“
Authors: D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas, T. Poskus.

10. 2019 06 01– 2019 06 05 American Society of Colon & Rectal Surgeons Annual Scientific Meeting (Cleveland – USA)
„What Determines Perfect Patient Evaluation of Surgery for Hemorrhoids – Results of Prospective Double Blind Randomized Trial“



ASCRS Best Paper Award

11. 2019 06 07 X Baltic-Belarusian Conference. Kaunas (Lithuania)
„Laser Haemorrhoidoplasty“
Authors: T. Poskus, D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas.

12. 2019 07 01 – 2019 07 03 Annual Meeting of The Association of Coloproctology of Great Britain & Ireland. Dublin(Ireland) – **Six best papers awards**

„Randomized double-blind controlled trial of laser hemorrhoidoplasty, excisional hemorrhoidectomy and recto-anal repair for symptomatic haemorrhoids“
Authors: T. Poskus, D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas.

13. 2019 09 25 – 2019 09 27 14th Scientific and Annual meeting European coloproctology association (ESCP), Viena (Austria)
„What determines perfect patient evaluation of surgery for hemorrhoids – results of prospective double blind randomized trial“
Authors: T. Poskus, D. Danys, G. Makunaite, A. Mainelis, E. Poskus, S. Mikalauskas, V. Jotautas, K. Strupas.

Materials and methods

The thesis is composed of three separate studies:

1. Evaluation of distant results of the initial experience of laser hemorrhoidoplasty
2. Evaluation of coagulation depth of laser hemorrhoidoplasty – an experimental study
3. Evaluation of the effectiveness and the safety of LHP, comparison of the recovery of patients after LHP and other surgical procedures – randomized double-blind prospective trial

3.1. Retrospective analysis

Consecutive patients, undergoing laser hemorrhoidoplasty operation for symptomatic hemorrhoids in 4 different institutions in Vilnius, Lithuania - Baltic-American Medical and Surgical Clinic, GK clinic, Northway Medical Centre and the Vilnius University Hospital Santara Clinics, - Lithuania from March 2011 to December 2014 were included in the study.

LHP was performed using a Ceralas Biolitec company diode laser of 1470 nm wavelength. Disposable LHP kit (Biolitec) was used, which contains sharp-tipped laser fiber and anoscope. Laser fiber was introduced into the opening until the level of hemorrhoidal pedicle and coagulation was activated. A total of 6 W 3 s pulses with 1-s pulse-pauses were used to coagulate the area of hemorrhoids.

The trial was approved by the Regional Bioethics Committee of Vilnius, Lithuania on the 6th of October, 2015, registration number 158200-15-792-322. All patients signed an informed consent form for participation in the study in addition to the consent form for the operation...

Demographic, symptom and disease characteristics, operative details and postoperative course data were collected from the medical records.

All patients were examined at 6 weeks postoperatively. All patients were sent postal or electronic mail questionnaires. They contained questions on pre- and post-operative symptoms, postoperative treatment and complications, duration and intensity of postoperative pain, additional post-operative treatment, fecal incontinence, patient evaluation of the procedure. Non-responders to postal questionnaires were contacted by phone.

Postoperative pain was evaluated using a visual analog score (VAS) from 0 (no pain) to 10 (maximum intensity pain). Jorge-Wexner score was used to evaluate postoperative fecal incontinence. This score evaluates the symptoms of fecal incontinence (incontinence to gas, liquid stools, and solid stool, use of a pad and adaptation to the symptoms of fecal incontinence) as well as the frequency of each of the previous symptoms. It gives the result from 0 (perfect continence) to 20 (complete incontinence).

Patient evaluation of operation was graded to perfect, good, satisfactory, bad, very bad; patients were also asked whether they would recommend this procedure to their relatives.

The trial was approved by the Regional Bioethics Committee of Vilnius, Lithuania on the 6th of October, 2015, registration number

158200-15-792-322. All patients signed an informed consent form for participation in the study in addition to the consent form for the operation.

The data were entered into a personal computer database and analyzed by SPSS software, version 17.0 (SPSS, Chicago, IL), by one participant of the study. We report most analyses as simple descriptive statistics. The chi-square test or Fisher's exact test was used to analyze the qualitative variables, and the Student's t-test or Mann–Whitney U test was used for the quantitative variables, depending on whether the data followed a normal distribution.

3.2. Experimental study

The research complied with all relevant national regulations and institutional policies for the care and use of animals.

Study sample

Twenty-four anorectums were excised approximately 5 cm in depth and 2 cm radius around the anus from the freshly slaughtered pigs. Twelve anorectums were taken from male and twelve from female pigs. The experiment was performed within two hours after excision to prevent tissue degradation; all measurements were performed at room temperature, which was 21° C.

Each specimen was assigned a number and divided into two or three parts and mixed up to get 54 samples. Male and female samples were divided equally into each group. Each sample was tagged with the number of the specimen and sex of the pig. For this experiment, 6, 8 and 10 Watt and 1, 2 and 3-second pulses were used. Each sample was randomly assigned to receive the laser power of 6, 8 or 10 W with 1, 2 or 3-second pulse duration. Six specimens were assigned to each laser parameter group, thus 54 experimental interventions were performed.

Experimental intervention

The procedure was performed using "Biolitec" Ceralas 1470nm diode laser with 6 mm optical fiber. All manipulations were performed by the same team lead by one surgeon (D.D.), experienced in laser hemorrhoidoplasty procedure to avoid variability that may result from different operators. Specimens were affected by different laser parameters. The operator inserted laser fiber perpendicular to the mucosa from outside, approximately 0.5 cm in length and 0.2 cm in depth (Figure 1). The insertion place was marked with a pin for identification during the pathological examination.

Each sample was evaluated after one and ten minutes to identify visual and palpable tissue changes. All changes were recorded.

Specimens were fixed on the plate to prevent shrinkage of tissue before fixing in formalin.

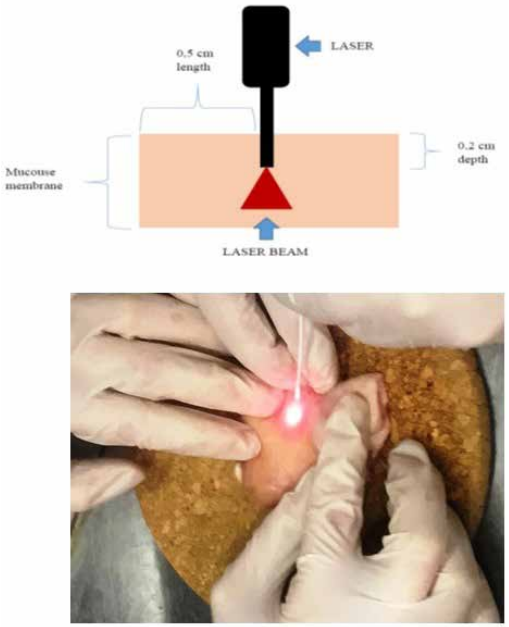


Figure 1: Schematic representation and technique of the experiment

Pathology evaluation

The pathologist was blinded to the parameters of intervention performed on the specimens. Four samples were excised from every specimen- about 2 cm in length, including all layers of the rectal wall for pathological evaluation. Two samples were created by cutting longitudinally to the direction of the laser insertion site; sections were performed next to each other. Two other samples were created by cutting vertically to the direction of laser insertion place, about 0.5- 1 cm away from the terminal site of laser coagulation. The area of the evaluation was 4 cm in longitudinal sections and 2 cm in vertical sections. All sections were prepared in the tissue processor, paraffin blocks of tissues were created. Each block was cut into sections of 3 μm in thickness and conventional hematoxylin-eosin staining was performed. Sections were evaluated under low- and high-power light microscopy by the same pathologist. Sections were observed at different magnifications (40× and 100×) for the measurement of the length of tissue injuries (Figure 2). The extension of tissue injuries was measured if the tissue was damaged through in one of four histopathological sections. All measurements were made using a ruler of a microscope.

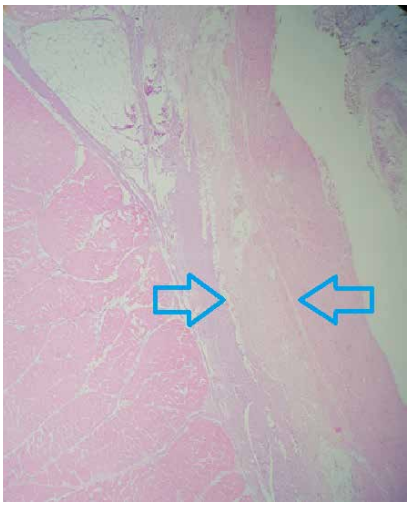


Figure 2: Sections stained with hematoxylin-eosin. Arrows indicate the coagulated area

All data were collected for evaluation. Statistical analysis was performed with *SAS On Demand for academics*, using multiway ANOVA, two-way ANOVA and Chi-square tests.

3.3. Prospective trial

This is a randomized, parallel-group (1:1:1), double-blinded, single-center prospective study. No changes in methods of the study were allowed after commencement. Flowchart of the study is presented in Figure 3. This study was performed in Vilnius University Hospital

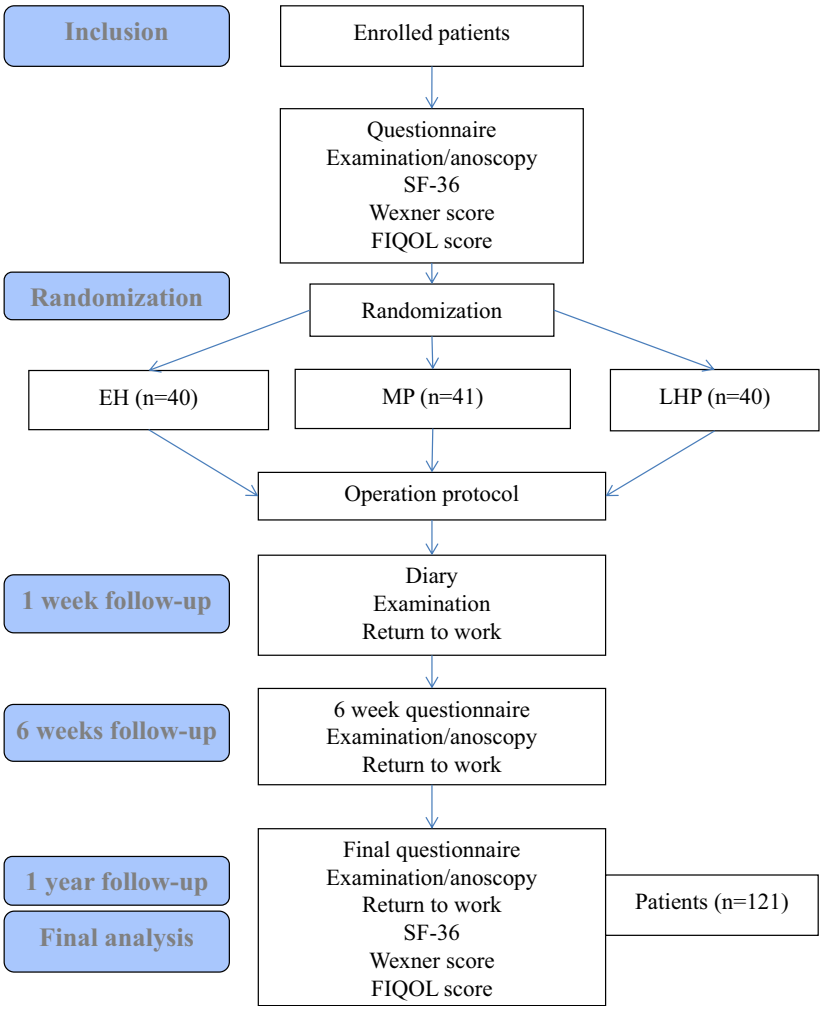


Figure 3: Flowchart of the trial

Santara Clinics, Vilnius, Lithuania. It is a large tertiary university hospital with a dedicated outpatient clinic. The trial was approved and registered at the Regional Bioethics Committee of Vilnius, Lithuania, on the 6th of October, 2015, registration number 158200–15–792-322. All patients signed the informed consent form for participation in the study in addition to the consent form for the operation.

Inclusion and exclusion criteria

Patients with symptomatic 2nd- or 3rd-degree hemorrhoids, in the 1st to 3rd risk group of ASA (American Society of Anesthesiologists), who consented to participate were included in the study. Exclusion criteria were 1st- or 4th-degree of hemorrhoids, pregnancy, patients with other anorectal diseases (fistula, abscess, rectal carcinoma, inflammatory bowel disease, etc.), patients after previous anal operations (except rubber band ligation, which should have occurred more than 3 months before the inclusion into the trial), and 4th or higher risk group of ASA.

Preoperative evaluation

The detailed physical and anorectal examination was performed with anoscopy and rigid proctoscopy in all cases, as well as colonoscopy if indicated. All patients filled a dedicated symptom questionnaire, which included questions on the intensity and frequency of hemorrhoidal prolapse, bleeding, itching, pain, and other symptoms. Every patient completed Wexner incontinence score, SF-36, and fecal incontinence quality of life (FIQOL) questionnaires before surgery.

Randomization, blinding, and concealment

The patients were randomized into three groups. The randomization sequence was computer-generated before the start of the trial. Every consecutive case history was assigned a randomization number (1, 2, or 3 for each treatment modality). It was written and sealed within the envelope and remained unknown neither to the patient nor to the treating physician, to avoid selection bias. In the operating room, after induction of anesthesia, the operating room junior staff was asked to

unseal the envelope, and the intervention was performed according to the procedure assigned. Pre- and postoperative patient management was as close to identical as we could make it in all three groups. The patient remained unaware of the procedure performed until the end of the study, 1 year after the operation. The case notes and discharge summary of the patient contained the note, saying that "the patient is included in the study of hemorrhoids, patient's number is X." This number was within the locked and coded database. The surgeon, who evaluated the result of the treatment remained blinded to the procedure performed. The patients were followed up by different surgeons (EP, VJ, and KS) than the ones operating. They had access to the patient notes but not to the coded database and were not able to know which procedure had been performed in a patient. In emergencies, unblinding of the patient and treating physicians was possible but was not required or performed in any of the patients.

Operative procedure

Patients were started on lactulose the day before the operation, which was continued after the operation to have regular bowel movements.

Preoperative intravenous antibiotic prophylaxis was given according to the hospital protocol, which was 1 g of cephazolin (2 g if a patient was over 80 kg of weight), 240 mg of gentamycin, and 500 mg of metronidazole (ciprofloxacin could be used if a patient was allergic to cephalosporins).

Each surgeon performing operative procedures (TP, DD, and SM) had personal experience of at least 50 operations of each modality. A 1-h seminar was conducted between all surgeons before the start of the trial to unify the technique of operative procedures.

All patients were photographed after induction of anesthesia before the start of the procedure and immediately after the procedure.

LHP was performed using a Ceralas diode laser of 1470 nm wavelength (Biolitec). Disposable LHP kit (Biolitec) was used, which contains sharp-tipped laser fiber and anoscope. Perianal skin immediately aboral to hemorrhoid was penetrated using needle tip cautery. Laser fiber was introduced into the opening until the level

of hemorrhoidal pedicle and coagulation was activated. A total of 8 W 3 s pulses with 1-s pulse-pauses were used to coagulate the area of hemorrhoids. A total of 4 mm of hemorrhoidal tissue is coagulated with one such pulse. A total of 250 J was the upper limit of energy delivered per 1 hemorrhoidal quadrant. Smaller hemorrhoids were treated with less energy. The procedure was repeated in the other three quadrants, thus treating all anal circumference.

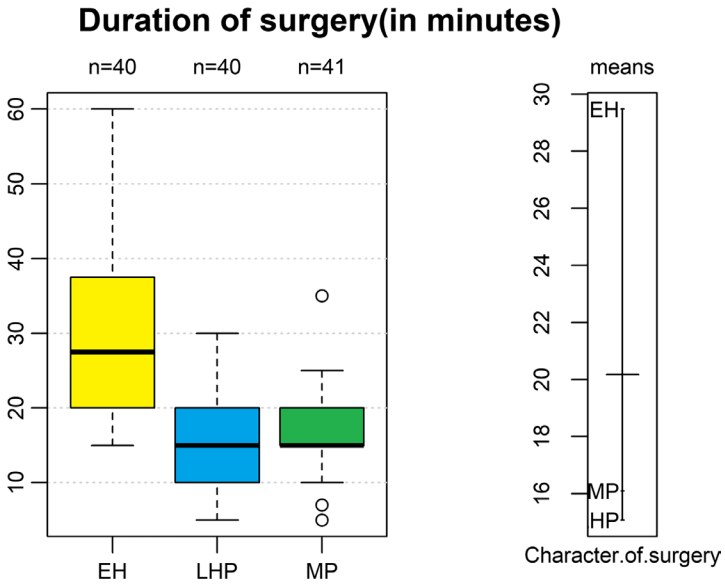


Figure 4: Duration of surgery

MP was performed as described by Schurmann JP et al. [8]. Ligations were placed in the area of visible hemorrhoidal tissue. It was started with a single suture ligation at the level of hemorrhoidal pedicle which should incorporate the feeding vessel and continued down until above the dentate line. The continuous suture was tied, thus lifting the prolapsing hemorrhoidal tissue.

Standard EH was performed up to the level of the hemorrhoidal pedicle, with ligation or suture ligation of the pedicle and meticulous hemostasis.

Follow-up

Follow-up was performed by the different surgeons to those performing the operations. Each of them had more than 25 years of experience of colorectal and hemorrhoidal surgery. The 1-h seminar was conducted, with them to unify the evaluation of the patients within the study. None of the evaluators knew which operation was performed, and they had no access to a coded database of operations performed. Patient documents only mentioned that they were included in the study and study number but not which operation had been performed.

Each patient was followed up at 1 and 6 weeks and after 1 year after the operation. Perianal examination with photographic documentation was performed during all visits. Anoscopy was performed during visits at 6 weeks and 1 year.

Each patient was asked to fill in the diary every day of the first postoperative week and present it at the first visit after 1 week. Symptom questionnaires were filled in during visits at 1 and 6 weeks and 1 year. Wexner incontinence score, FIQOL, and SF-36 were filled in by the patient during the visit at 1 year.

Outcomes

The primary outcome of the study was the recurrence of rectal bleeding and prolapse at 1 year after the operation requiring any kind of medical attention or treatment (visit to the doctor or pharmacy, medical, invasive, or surgical treatment).

Secondary outcomes of the study were time to return to work or regular activity, intensity, and duration of perianal pain after the operation (in days), Wexner fecal incontinence score at the 1-year visit, QOL based on SF-36 questionnaire and FIQOL at 1 year, and evaluation of the operation by the patient on a visual analog scale from 1 to 10 at 1-year visit.

No change in outcomes or outcome evaluation was allowed after the commencement of the study.

Statistical methods

The sample size required for the study was calculated using the flexible statistical power analysis program for the social, behavioral, and biomedical sciences, G*Power V 3.1.9.2.

A sample size of 40 patients in each randomized group provides 84% power to detect an effect size of 0.30 in the recurrence of symptoms at 1 year across the randomized groups, with an alpha of 0.05.

We used Shapiro-Wilk and Kolmogorov-Smirnov (K-S) tests for the verification of the normality of variables. A statistically significant relationship between the related variables was determined using several criteria. For the variables that satisfied the condition of normality, we used parametric ANOVA criteria, which is also called the Fisher analysis of variance, and it is the extension of the t and z tests. For the variables that did not satisfy the condition of normality, we used nonparametric criteria based on the $\chi 2$ criterion for the interval and categorical variables, i.e., the Kruskal-Wallis test, which is the nonparametric test equivalent to the one-way ANOVA, and an extension of the Mann-Whitney U test to allow the comparison of more than two independent groups (in our case, we have three independent patient groups divided by the type of surgery). When the data were described in a four-digit (2×2) frequency tables and when at least one expected value was less than 5, Fisher's exact test was additionally calculated. We used the Pearson chi-squared criterion to compare two independent groups. We used the Wilcoxon test to compare two dependent groups. We used the marginal homogeneity test to compare the categorical data. We used Student's t-test to compare the data that satisfied the condition of normality. The degree of linear dependencies of variables (correlation coefficients) of the Spearman or Kendall τ-b was calculated for interval variables, when the normality was not satisfied and for the rank variables.

The dependency between variables can be considered statistically insignificant when the two-sided p-value (exact sig. (2-sided), approx sig.) of all criteria in this category is higher or equal than

the established significance level of 0.05 ($p \geq 0.05$) and statistically significant when $p < 0.05$. The confidence interval (CI) was calculated for a 95% confidence level.

Statistical analysis was performed using software packages, i.e., R statistical software package V 3.5.3 (2019-03-11) (©The R Foundation for Statistical computing), R studio V 1.1.463–© 2009–2018 R studio Inc., IBM SPSS Statistics V.23.

Results

4.1. Retrospective study

Two-hundred and twenty-eight two patients were included in the study over the three-and-a-half-year period. Mean age was 44 (20-83) years, 110 (48%) were women and 118 (52%) were men. 61% of patients had third-degree hemorrhoids (Figure 5). Four surgeons were performing all operations.

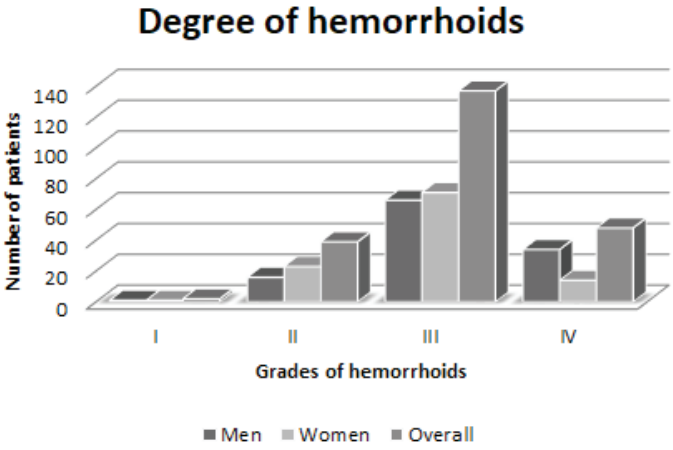


Figure 5: Grades of hemorrhoids in the study population

Table 1. Patients who responded to the questionnaire

	Women (n)	Men (n)	Overall (n)
All patients	110	118	228 (100%)
After 6 weeks	95	87	182 (79,8%)
Late results	45	59	104 (45,6%)

Operative details. The duration of the operation was 14.4 (10-35) minutes. 855 (510-1586, median – 828) Joules of energy were used per patient. All perianal circumference was treated, with 215 Joules of energy per hemorrhoidal quadrant. Bigger hemorrhoids were treated with more energy, however, the choice was subjective based on the surgeon's preference. Coagulation (whitening) of hemorrhoidal tissue was avoided, as it was considered overtreatment. 108 patients (47.2%) underwent apical suture of hemorrhoidal pedicle before or after laser coagulation. 58 patients (25.4%) underwent excision of enlarged perianal skin in addition to laser coagulation (Figure 6). No intraoperative complications occurred.

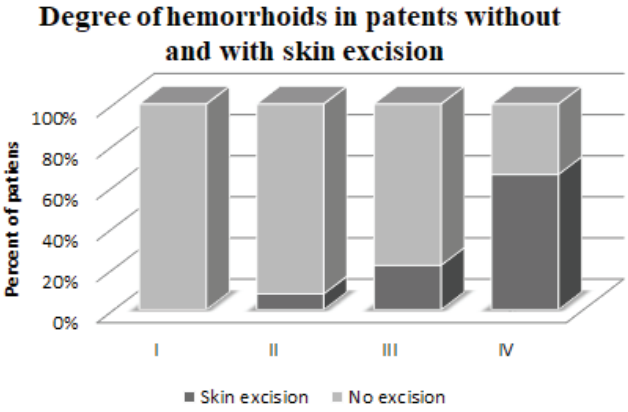


Figure 6: The Initial degree of hemorrhoids in patients without and with skin excision

4.2. Experimental study

The results of the extent of soft tissue coagulation injury in the specimens are presented in table 1. Soft tissue damage mostly depends on laser exposure time (p= 0.0027), with no significant difference between laser power used (p= 0.5086). Extended laser exposure time is a cause of longer tissue damage. In the 1-second group, tissue damage on average reaches 1.12 mm, in 2 seconds group – 2.06 mm and in 3 seconds group – 3.93 mm. The depth of tissue damage within various laser power groups (6W, 8W, and 10 W) varies on average from 2.06 mm to 2.89 mm, with no significant difference between groups (p= 0.5086). The difference in length of tissue damage between different power intensity groups was not statistically significant (p>0.05).

No changes were palpable within 1 minute after laser application in all groups. Palpable changes10 minutes after laser application were related to the power of laser exposure: 6W – 0%, 8W – 33.3%, 10W – 66.7% (p=0.039). No visible changes were noticed during the visual evaluation of samples after 1 and 10 minutes.

The results of the extent of soft tissue coagulation injury in the specimens are presented in table 2.

Table 2: Data of tissue damage, palpable and visual changes in different groups

Laser power (watts)	Exposure time (Sec)	Average of tissue damage (mm) +/- standard deviation (mm)	Medians of tissue damage (mm)	Palpable changes	Visible changes
6	1	1,62 +/- 1,99	0,85	0	0
6	2	1,78 +/- 1,06	2,0	0	0
6	3	2,78 +/- 1,97	2,95	0	0
8	1	0,63 +/- 0,99	0,15	0	0
8	2	2,67 +/- 1,88	2,7	0	0
8	3	3,15 +/- 3,18	2,75	1	0
10	1	1,12 +/- 2,5	0	0	0
10 10	2 3	1,72 +/- 1,64; 5,85 +/- 3,87	1,55; 5,6	1; 1	0; 0

4.3. Prospective trial

One hundred and twenty-one patients were included in the study, 40 into the LHP group, 40 into the EH group, and 41 into the MP group from April 2016 to April 2017. One-year follow-up was completed in April 2018. All included patients participated in the scheduled visits and completed the follow-up as required per protocol (Table 3).

Table 3: Demographic and preoperative clinical characteristics of the groups

		Operation						
		LHP, n=40		**EH, n=40**		**MP, n=41**		
		N	**%**	**N**	**%**	**N**	**%**	***p***
Age		47±13		45±12		49±13		0,420
Sex	Women	13	32,5%	19	47,5%	19	46,3%	0,349
	Men	27	67,5%	21	52,5%	22	53,7%	
Degree of hemorrhoids	2nd	10	25,0%	7	17,5%	10	24,4%	0,669
	3rd	30	75,0%	33	82,5%	31	75,6%	
Concomittant diseases	Absent	29	72,5%	24	60,0%	21	51,2%	0,143
	Present	11	27,5%	16	40,0%	20	48,8%	
Bleeding	Absent	6	15,0%	5	12,5%	4	9,8%	0,742
	Present	34	85,0%	35	87,5%	37	90,2%	
Prolapse	Absent	8	20,0%	8	20,0%	6	14,6%	0,769
	Present	32	80,0%	32	80,0%	35	85,4%	
Itching	Absent	30	75,0%	33	82,5%	36	87,8%	0,325
	Present	10	25,0%	7	17,5%	5	12,2%	
Pain	Absent	29	72,5%	26	65,0%	26	63,4%	0,651
	Present	11	27,5%	14	35,0%	15	36,6%	
Fecal incontinence	Absent	39	97,5%	40	100,0%	41	100,0%	0,661
	Present	1	2,5%	0	0,0%	0	0,0%	
Other symptoms	Absent	29	72,5%	27	67,5%	27	65,9%	0,799
	Present	11	27,5%	13	32,5%	14	34,1%	

Baseline demographic and clinical characteristics of the included patients are presented in Table 3. There were no statistically significant

differences in demographic and clinical characteristics between the groups at the start of the study.

The operation took 15 min (10–20) in the LHP group, 29 min (20–38) in the EH group, and 16 min (15–20) in the MP group (Fig. 4), $p < 0.001$.

No significant adverse events occurred after operations. There were no cases of wound infection in our study. No strictures developed in any patients within the duration of the follow-up.

The outcomes of the study are presented in Table 4. The primary outcome—the recurrence of the symptoms of hemorrhoids requiring any kind of treatment—was the best in the EH group, with no patients (0%) having to seek medical attention or treatment for perianal symptoms within 1 year. This was better than in the LHP group (10%), and MP group (22%), $p < 0.004$. Recurrence of bleeding was observed in 15% in EH group, 12.5% in the LHP group, and 31.7% in the MP group, $p = 0.062$. Recurrent prolapse occurred in 5% after EH group, 15% in LHP group, and 17.1% in MP group, $p = 0.215$. There were 85.2% completely symptom-free patients after EH, 72.5% after LHP, and 58.5% after MP, $p = 0.057$.

A comparison of postoperative pain intensity during the first week is presented in Fig. 7. LHP and MP resulted in lower postoperative pain at rest and on defecation than after EH. Patients after LHP and MP used analgesic medications for fewer days than after EH, $p < 0.001$ (Fig. 8). Patients after LHP returned to work or regular activity twice faster than after EH and faster than after MP, $p < 0.001$ (Table 4).

Results of the QOL of patients are presented in Table 4. General health evaluation of the SF-36 score was better in the EH group 60 (25–100) than in LHP 50 (20–80) or MP 50 (25–100) groups, $p = 0.023$.

The severity of symptoms of fecal incontinence on the Jorge-Wexner score was reduced 1 year after surgery in all the groups, and there were no differences in self-evaluation of incontinence between the groups of patients.

Evaluation of operation by the patients after 1 year is presented in Figure 9. LHP was evaluated by the patients as the best operation.

Table 4: Outcomes of the study (statistically significantly best outcomes are in italics)

		Operation						
		LHP, n=40		**EH, n=40**		**MP, n=41**		
		N	**%**	**N**	**%**	**N**	**%**	***p***
Recurrence at 1 year	no	36	90,0%	40	100,0%	32	78,0%	**0,004**
	yes	4	10,0%	**0**	**0,0%**	9	22,0%	
Recurrent bleeding	no	35	87,5%	34	85,0%	28	68,3%	0,062
	yes	**5**	**12,5%**	**6**	**15%**	13	31,7%	
Recurrent prolapse	no	34	85,0%	38	95,0%	34	82,9%	0,215
	yes	6	15%	**2**	**5%**	7	17,1%	
Completely symptom-free	yes	29	72,5%	33	82,5%	24	58,5%	0,057
	no	11	27,5%	**7**	**17,5%**	17	41,5%	
Mean postoperative pain intensity at rest, VAS (mean, standard deviation)		**3,1**		5,0		**2,7**		**<0,001**
Mean postoperative pain intensity during defecation, VAS (mean, standard deviation)		**3,8**		6,4		**4,0**		**<0,001**
Analgesic medication use (days, (interquartile range)		**5 (3-7)**		8 (6-11)		**5 (2-7)**		**<0,001**
Time to return to regular activity or work, days (interquartile range)		**15 (5-14)**		30 (14-35)		24 (9-30)		**<0,001**
Wexner score		3 (0-5)		3 (0-5)		2 (0-2)		0,125
Patient‘s subjective evaluation of operation 0-10 VAS (Interquartile range)		**10 (10-10)**		9 (8-10)		9 (9-10)		**0,002**
Quality of life (SF-36), mean (interquartile range)								
Physical functioning		89 (93-100)		89 (85-100)		92 (95-100)		0,976
Role functioning/physical		84 (100-100)		90 (100-100)		87 (100-100)		0,735
Role functioning/emotional		83 (100-100)		84 (67-100)		90 (100-100)		0,289
Energy/fatigue		49 (40-55)		46 (40-50)		45 (40-50)		0,462
Emotional well-being		57 (50-62)		53 (48-60)		49 (40-56)		0,479
Social functioning		42 (44-55)		41 (44-55)		50 (44-56)		0,859
General health		60 (43-60)		58 (50-70)		53 (40-65)		**0,023**
Health change		86 (75-100)		83 (75-100)		82 (75-100)		0,392
FIQOL, mean (interquartile range)								
Lifestyle		4 (4-4)		4 (4-4)		4 (4-4)		0,652
Coping/behavior		4 (4-4)		4 (4-4)		4 (4-4)		0,759
Depression/self perception		4 (4-4)		4 (4-4)		4 (4-4)		0,587
Embarrassment		4 (3-4)		4 (4-4)		4 (4-4)		0,144

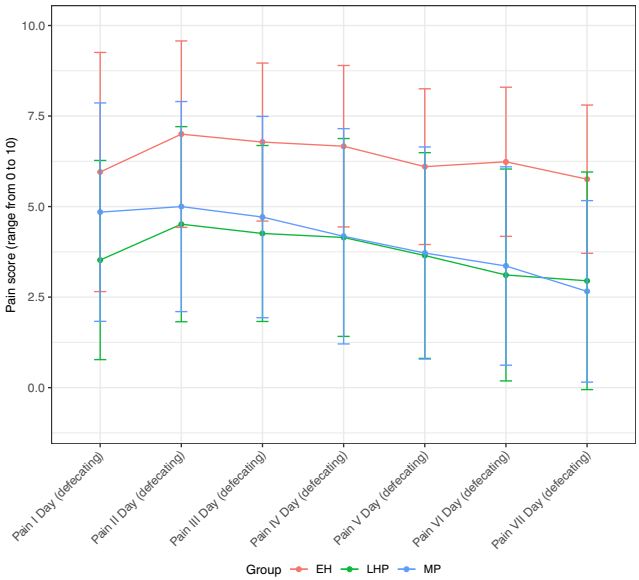
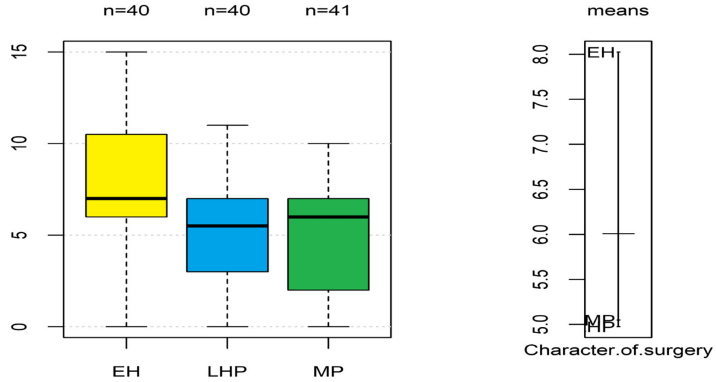


Figure 7: Pain scores within the first week of operation



	EH	LHP	MP	Total
mean	8.03	4.97	5.05	6.01
median	7.00	5.50	6.00	6.00
sd	3.65	2.74	3.02	3.44
IQR	4.25	4.00	5.00	3.00
n	40	40	41	121
Min-Max	0-15	0-11	0-10	0-15

Kruskal-Wallis chi-squared = 17.075, df = 2, p-value = 0.000196<0.05. The statistically significant relationship between the type of surgery and the change of health exist.

Figure 8: Postoperative use of analgetic medications

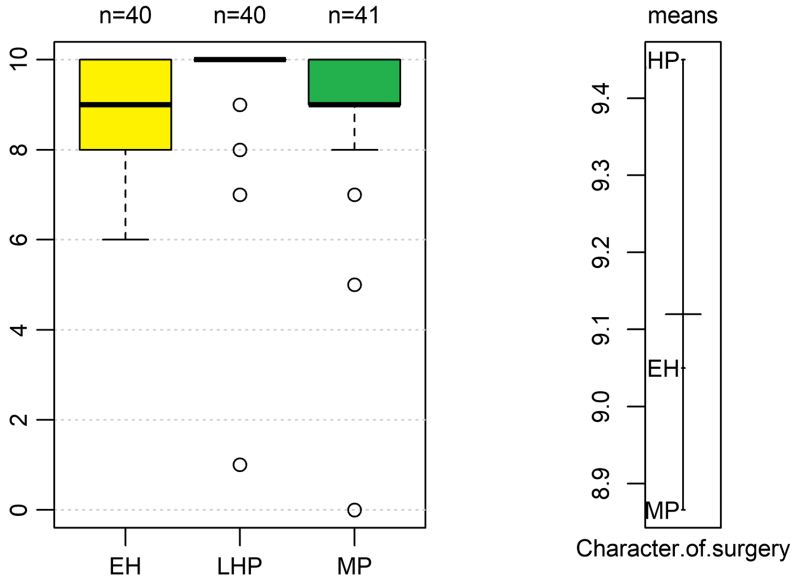


Figure 9: Evaluation of operation by the patient after 1 year

Discussion

Each of the techniques improved the patient's condition, however with different rates of success and side effects. The study found that the most effective of the three techniques was EH, which resulted in the least number of recurrent symptoms of prolapse and bleeding and in no cases of recurrent symptoms requiring treatment, which was the primary outcome of the trial. It was also associated with the best overall QOL as measured by SF-36. MP was the least effective treatment, with the largest percentage of recurrent bleeding, prolapse, and the largest percentage of patients, requiring treatment. LHP was better than MP in terms of recurrence, requiring treatment, recurrent bleeding, and the percentage of completely symptom-free patients.

LHP and MP resulted in significantly shorter duration and lesser intensity of pain than EH. Return to work after LHP was almost twice faster than after EH and significantly faster than MP.

Despite reduced effectiveness, LHP resulted in significantly better patient evaluation on the 10-point visual analog scale than EH or MP.

Significant effort was put to avoid bias within the trial—it was investigator, patient, and evaluator blinded, with computer-generated randomization sequence and complete follow-up. The technique of operation and evaluation of results were mastered and agreed upon among the study researchers before the trial.

However, this is a single-center trial, and as such, it has limitations when translated to wider populations of patients, surgeons, and institutions. It has to be validated more widely and within larger patient cohorts to confirm the findings.

Measuring outcomes in trials for the hemorrhoidal disease is difficult, and validated symptom scores—Sodergren score [11] and Hemorrhoidal Disease Symptom Score and Short Health ScaleHD [12]—were developed to help in this regard. Unfortunately, our study was planned before their publication.

Our study included only the patients with highly symptomatic grade 2 and 3 hemorrhoids, who were considering hemorrhoidectomy and were not deemed suitable for less invasive treatment, such as rubber band ligation. Patients with grade 4 prolapse were excluded from the study, as, based on our experience, LHP is not a suitable technique for grade 4 prolapse.

The interesting finding is the evaluation of the technique by patients on a visual analog scale. Not the most effective treatment was the best according to this measure, and it may probably be expected. In a non-malignant and not life-threatening situation, the choice of treatment and the evaluation of the treatment is most likely based on combined outcome of effectiveness and invasiveness of the procedure, the more effective treatment method and the less morbidity it carries with it, the better the treatment will be. Very effective treatment of circumferential hemorrhoidectomy (Whitehead) is almost never used because of its significant postoperative morbidity.

It is important to note that laser hemorrhoidoplasty is a more expensive technique than the other two, requiring the use of disposable fiber and laser generator, but the cost of the procedure may be reduced

by the reduced duration of the operation. However, costs were not evaluated within the study.

There is an inherent risk of bias within the trial because of industry support. This was a university-initiated, but an industry-sponsored trial, where a company (Biolitec) provided laser generator for the duration of the trial and 40 laser kits with an overall price of approximately 10,000 euros. The sponsoring company, however, did not participate in any other way in the design, performance, or analysis of the trial.

There is still no agreed protocol of LHP operation, as different surgeons use different amounts of energy (less vs more than 500 J), different locations (symptomatic hemorrhoids vs circumferential coagulation), and different fiber entry points (skin vs hemorrhoid). We have earlier reported on our technique [6], and we think that the technique described above produces the best outcomes in LHP. This, however, remains to be validated by other authors. In conclusion, we found that laser hemorrhoidoplasty is a safe, minimally invasive option for hemorrhoids, more effective than MP, and less effective than EH. Patients evaluate this technique better than the other two.

Conclusions

1. Technical aspects, that provide best outcomes for the patients, are: sparing of perianal skin – avoid excision and coagulation; limited use of a maximum of 200-300 J of energy for each hemorrhoidal quadrant; circumferential perianal submucosal coagulation; no necessity of pedicle suture or ligation.

2. The laser beam of 1470 nm wavelength 8 watts 3 seconds coagulate perianal tissue diameter of 4 mm. The next area of coagulation should be placed 5 mm away from the previous beam.

3. LHP is less effective than EH and more effective than HAL. LHP is less painful and creates less discomfort for the patients than EH.

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