COVER PAGE
Research Protocol

OFFICIAL TITLE: Intraoperative neuromonitoring of pelvic autonomous nerve plexus during total mesorectal excision

BRIEF TITLE: Intraoperative neuromonitoring during TME

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1. Introduction

1.1 Literature Review

The introduction of Total Mesorectal Excision (TME) resulted to the improvement of the overall survival and local recurrence rates of rectal cancer patients [1]. However, the associated urogenital and anorectal functional deficit has a significant effect on the postoperative quality of life of the patient [2]. More specifically, the postoperative rates of urogenital and sexual dysfunction that have been reported in the various series, are estimated at the levels of 70% and 90%, respectively. Additionally, TME is associated with the development of the low anterior syndrome (LARS). LARS is characterized by the onset of fecal incontinence, due to injury in the autonomic nerve plexuses that innervate the internal anal sphincter (IAS); who in turn is responsible for the 52-85% anal resting tone [2]. According to a study by Wallner et al., 38.8% and 33.7% of patients with normal preoperative urogenital function, developed postoperative stool and urine incontinence, respectively [3].

It becomes apparent that the incidence rates of these complications vary between the various series, mainly due to their small sample size, the lack of comparative data, the short follow up period, the use of non-validated tools and their retrospective design [2]. Several predictive factors of these adverse events have been suggested in the literature, including old age, tumors located less than 12 cm from the anal verge, preoperative radiotherapy and injury to the pelvic autonomous nerves [2].

The clinical and functional anatomy of the pelvis are quite complex. The inferior hypogastric plexus is formed by the parasympathetic pelvic nerves, deriving from the I2-I4 and the sympathetic hypogastric nerve. It is a neural anatomic structure that carries organ-specific nerve fibers [3]. Visual identification of the plexus is quite difficult, for various reasons, including the complexity of the nerve distribution, the narrow pelvis, the voluminous mesorectum, obesity, previous pelvic operations, neoadjuvant radiotherapy, locally advanced tumors, intraoperative bleeding and the extensive use of diathermy [4]. According to the current literature, identification of the autonomous pelvic plexus is achievable in 72% of cases, whereas partial localization is possible only in 10.7% of patients [5].

Theoretically, intraoperative neuromonitoring of the pelvic autonomous nerves (pIONM), could quantify intraoperative nerve injuries, while in parallel, contribute to the improvement of the patients' postoperative quality of life [6]. Several pIONM techniques have been described, including intra-urethral and intra-vesical pressure measurements [1]. However, it was found that intermittent neuromonitoring objectifies the macroscopic integrity assessment of the sacral plexus. Recently, a promising technique, based on the simultaneous electromyography of the IAS and bladder manometry was developed, with encouraging results. During pIONM, the surgeon delivers electric stimuli to the autonomic nerve structures through a hand-held stimulator [7]. At the same

time, electromyogram changes of the IAS and the external anal sphincter (EAS), alongside intravesical pressure gradients are assessed [7].

Intraoperative neuromonitoring has been evaluated in several experimental studies. In the study by Kneist et al., intraoperative simulation of the inferior hypogastric plexus with a bipolar stimulator resulted to the appearance of a measurable and repeatable electromyographic signal from the IAS [6].

Simultaneous signal processing from the IAS and urinary bladder, improves the, overall, diagnostic accuracy of these techniques [8]. Stabilization of the electrodes outside the surgical field, has been, also, suggested by some researchers [7, 9]. Additionally, experimental studies evaluated the role of pIONM in the minimal invasive TME [10].

Moreover, the effectiveness of this technique has been a research subject in multiple clinical trials. In the study by Kauff et al., where 85 patients underwent TME, after logistic regression, no use of pIONM and neoadjuvant radiotherapy, were identified as independent prognostic factors of postoperative urogenital deficit [2]. Furthermore, the use of pIONM, was associated with a 100% sensitivity and a 96% specificity for the postoperative development of urogenital and anorectal functional complications [11].

The application of pIONM has been also suggested in the laparoscopic and robotic TME, using specially designed stimulators [12–14]. In the study by Zhou et al., preservation of the plexus was achieved in 51.7% of patients submitted to a laparoscopic low anterior resection for rectal cancer. During one year follow-up, patients receiving pIONM, displayed a superiority in terms of postoperative urogenital function, as assessed by the IIEF, IPSS and FSFI questionnaires [15].

2. Objective

2.1 Study Aim

The purpose of this research protocol is the evaluation of the improvement of the anorectal and urogenital urinary function, alongside the postoperative quality of life after the application of pIONM in patients submitted to TME for rectal cancer.

3. Materials and Methods

3.1 Study Sample

The sample of the present study will consist of males and females, 18-90 years old.

3.2 Pathology

This study will include rectal cancer patients, who will be submitted to TME, regardless of their neoadjuvant therapy status

3.3 Inclusion/Exclusion Criteria

The following inclusion criteria will be considered:

- Histologically confirmed rectal cancer
- Surgical resection with TME
- <90 years old
- Signed informed consent

The following exclusion criteria will be considered:

- Emergency operation
- Presence of pacemaker
- Partial mesorectal excision
- Sepsis or systematic infection
- Physical or mental impairment
- Pregnancy or nursing
- Insufficient preoperative data for the urogenital/ anorectal function
- Lack of compliance with the research process

3.4 Interventions

All patients will be submitted to a low anterior resection, depending on the location of the tumor. The operations will be performed in an open or laparoscopic approach. TME will be completed by the same surgical team, with an adequate experience in colorectal and pelvic operations.

Preservation of the autonomous pelvic nerve plexus will include identification and mapping of the superior hypogastric plexus, hypogastric nerves, inferior hypogastric plexus, and pelvic nerves. To protect the superior hypogastric plexus, the inferior mesenteric artery will be ligated 1.5cm distal to its protrusion. The inferior hypogastric plexus above the aorta, alongside its lateral branches, will be

identified and preserved through sharp dissection of the lateral parietal pelvic fascia. Moreover, careful sharp dissection of the Denonvillier fascia will be, also, performed [16].

3.5 Experimental Arms

This study will include two arms. In the first arm, pIONM will be introduced, for the localization and preservation of the pelvic nerve structures. In the second arm, though, no pIONM will be applied.

For the implementation of pIONM, a special device, that allows simultaneous monitoring of sphincter signals and bladder manometry, will be introduced. This device will employ the placement of a bipolar electrode in the internal and external anal sphincter. Moreover, another electrode will be placed on the surrounding tissues. For bladder manometry, the catheter will be connected to the pressure sensor, and subsequently to the pIONM monitor [17]. Intraoperatively, depending on the approach (open or laparoscopic), the respective bipolar stimulator will be used. As soon as the stimulator comes in contact with nerve tissue, an audible signal will be produced. The successful nerve stimulation and the increased activity of the respective muscle groups will be, automatically detected and recorded [2].

Prior to the initiation of pIONM, urinary bladder will be drained and filled with 200 ml R/L. The pIONM parameters will be the following: 1-25 mA current, 30 Hz frequency and 200 μs monophasic pulses [11].

3.6 Anesthesia

All patients will receive general anesthesia, prior to the initiation of the surgical procedure.

3.7 Primary Endpoint

- Change in the quality of life of the patient at 3 months postoperatively, based on the SF-36 questionnaire. Change in the quality of life of the patient, at 3 months postoperatively, compared to the respective preoperative measurements, based on the Short Form 36 (SF-36) questionnaire [Time Frame: Preoperatively, 3 months postoperatively]. SF-36: Short Form Survey. Minimum Value: 0. Maximum Value: 100. Higher scores indicate a better outcome

3.8 Secondary Endpoints

- Operative time. The total operative time will be recorded. Measurement unit: minutes [Time Frame: Intraoperative period]

- Intraoperative bleeding. The total intraoperative blood loss volume will be recorded. Measurement unit: mL [Time Frame: Intraoperative period]
- Postoperative discharge time. Postoperative time that the patient can be safely discharged. Measurement unit: hours. The patient will be discharged, when it is ensured that is medically safe to be released. In particular, as the exit time of the patient, will be regarded the time that the patient will fulfil the Clinical Discharge Criteria. More specifically, the patient should meet the following: steady vital signs, be oriented, without nausea or vomiting, mobilized with a steady gait, without a significant bleeding [Time Frame: Maximum time frame 15 days postoperatively]
- Postoperative complications. Occurrence of postoperative complications (based on Clavien Dindo classification [18]). If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO' [Time Frame: 1 month postoperatively]
- Negative resection margin. Occurrence of negative resection margin. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO' [Time Frame: 1 month postoperatively]
- Local recurrence. Occurrence of local recurrence. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO' [Time Frame: 1 year postoperatively]
- Bladder capacity. Urodynamic assessment [19]. Evaluation of bladder capacity. Measurement unit: ml [Time Frame: Preoperatively and 2 months postoperatively]
- Bladder compliance. Urodynamic assessment [19]. Evaluation of bladder compliance. Measurement unit: ml/cm H2O [Time Frame: Preoperatively and 2 months postoperatively]
- Detrusor pressure at maximum flow. Urodynamic assessment [19]. Evaluation of detrusor pressure at maximum flow. Measurement unit: cm H2O [Time Frame: Preoperatively and 2 months postoperatively]
- Maximum urinary flow rate. Urodynamic assessment [19]. Evaluation of maximum urinary flow rate. Measurement unit: ml/s [Time Frame: Preoperatively and 2 months postoperatively]
- Voiding volume. Urodynamic assessment [19]. Evaluation of voiding volume. Measurement unit: ml [Time Frame: Preoperatively and 2 months postoperatively]
- Post-void residual. Urodynamic assessment [19]. Evaluation of post-void residual. Measurement unit: ml [Time Frame: Preoperatively and 2 months postoperatively]

- Anal canal resting phase pressure. HR-ARM assessment. Evaluation of anal canal resting phase pressure. Measurement unit: mmHg [Time Frame: Preoperatively and 2 months postoperatively]
- Sphincter zone length. HR-ARM assessment. Evaluation of sphincter zone length. Measurement unit: cm [Time Frame: Preoperatively and 2 months postoperatively]
- Short squeeze test. HR-ARM assessment. Evaluation of short squeeze (5sec) pressure. Measurement unit: mmHg [Time Frame: Preoperatively and 2 months postoperatively]
- Long squeeze test. HR-ARM assessment. Evaluation of long squeeze (30sec) pressure. Measurement unit: mmHg [Time Frame: Preoperatively and 2 months postoperatively]
- Cough test. HR-ARM assessment. Evaluation of cough test (0 and 50 ml). If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'[Time Frame: Preoperatively and 2 months postoperatively]
- Push test. HR-ARM assessment. Evaluation of push test (0 and 50 ml). If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO' [Time Frame: Preoperatively and 2 months postoperatively]
- RAIR test. HR-ARM assessment. Evaluation of rectoanal inhibitory reflex test (20 and 50 ml). If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO' [Time Frame: Preoperatively and 2 months postoperatively]
- Difference in the quality of life of the patient, based on the SF-36 questionnaire [20]. Difference in the quality of life of the patient, at 6, 12, 24 months postoperatively, compared to the respective preoperative measurements, based on the Short Form 36 (SF-36) questionnaire [Time Frame: Preoperatively, 6, 12, 24 months postoperatively] SF-36: Short Form Survey. Minimum Value: 0. Maximum Value: 100. Higher scores indicate a better outcome
- Difference in the erectile function of the patient, based on the IIEF questionnaire [21, 22]. Difference in the erectile function of the patient, at 3, 6, 12, 24 months postoperatively, compared to the respective preoperative measurements, based on the International Index of Erectile Function (IIEF) questionnaire [Time Frame: Preoperatively, 3, 6, 12, 24 months postoperatively] IIEF: International Index of Erectile Function. Minimum Value: 0. Maximum Value: 5. Higher scores indicate a better outcome.
- Difference in the sexual function of the patient, based on the FSFI questionnaire [23, 24]. Difference in the sexual function of the patient, at 3, 6, 12, 24 months postoperatively, compared to the respective preoperative measurements, based on the Female Sexual

Function Index (FSFI) questionnaire [Time Frame: Preoperatively, 3, 6, 12, 24 months postoperatively] FSFI: Female Sexual Function Index. Minimum Value: 2. Maximum Value: 36. Higher scores indicate a better outcome.

- Difference in the prostate symptoms of the patient, based on the IPSS questionnaire [25, 26]. Difference in the prostate symptoms of the patient, at 3, 6, 12, 24 months postoperatively, compared to the respective preoperative measurements, based on the International Prostate Symptom Score (IPSS) questionnaire [Time Frame: Preoperatively, 3, 6, 12, 24 months postoperatively] IPSS: International Prostate Symptom Score. Minimum Value: 0. Maximum Value: 35. Higher scores indicate a worse outcome
- Difference in the low anterior syndrome symptoms of the patient, based on the LARS questionnaire [27, 28]. Difference in the low anterior syndrome symptoms of the patient, at 3, 6, 12, 24 months postoperatively, compared to the respective preoperative measurements, based on the Low Anterior Resection Syndrome (LARS) questionnaire [Time Frame: Preoperatively, 3, 6, 12, 24 months postoperatively] LARS: Low Anterior Resection Syndrome. Minimum Value: 0. Maximum Value: 42. Higher scores indicate a worse outcome.

3.9 Estimation of Study Sample Size

Sample size estimation was based on the primary endpoint. Based on the current literature, Physical Functioning levels at 3 months after low anterior resection, were estimated at 72(26) [29]. The application of pIONM resulted to a significant reduction of urogenital functional deficits (20% versus 51%, and 56% versus 90%, respectively) [2].

Therefore, for the design of a comparative study, with alpha=5%, beta=80%, and a 30% anticipated increase in PF, the estimated sample in each group is 22 patients. Therefore, the required total sample size is 44.

3.10 Randomization

The randomization of the patients will be performed using a dedicated software with a 1:1 allocation ratio. Furthermore, the allocation group will be concealed with opaque envelopes, who will be opened preoperatively upon the entry of the patient into the surgical room.

3.11 Blinding

The patient will be blinded regarding the allocation group. Blinding will not exist at the level of the surgeon, the anesthesiologist, and the investigator responsible for the data recording.

3.12 Urodynamic Examination

Urinary bladder function of all patients will be evaluated by urodynamic examination. Urodynamic evaluation will be performed preoperatively and at two months postoperatively. Assessment parameters will include bladder capacity (mL), bladder sensation, detrusor activity during bladder filling, bladder compliance (mL/cm H2O), detrusor pressure at maximum flow (cm H2O), maximum urinary flow rate (ml/s), voiding volume (ml) and post-void residual (ml). Urodynamic evaluation will be performed according to the International Continence Society Good Urodynamic Practices and Terms, by a specialized urologic team in General Hospital of Larissa [19].

3.13 Anorectal Manometry

HR-ARM evaluation will be performed in a specialized outpatient office of the Gastroenterology Department, in the University Hospital of Larissa. HR-ARM interpretation will be based on the International Anorectal Physiology Working Group (IAPWG) guidelines [31]. Two hours prior the examination, the patient will receive a fleet enema. Upon arrival, the HR-ARM transducer will be prepared and calibrated (Manoscan AR High-resolution catheter, Medtronic, USA). The patient will be placed in a lateral position and the catheter will be introduced in the anus. HR-ARM recording (Manoscan Acquisition Software, Medtronic, USA) will include the following parameters: anal canal resting phase pressures and sphincter zone length, short squeeze test (5 sec x 3), long squeeze test (30 sec x 1), cough and push test (0 and 50 ml balloon) and rectoanal inhibitory reflex test (RAIR test at 20 and 50 ml).

3.14 Discharge Criteria

The patient will be discharged when it is ensured that is medically safe to be released. The exit time will be regarded as the time that the patient will fulfill the Clinical Discharge Criteria. More specifically, the patient should display the following: steady vital signs, fully oriented, without nausea or vomiting, mobilized with a steady gait and without a notable bleeding [32].

3.15 Follow up

Postoperative complications will be evaluated at one month, postoperatively. In parallel, the histopathology report and the adjuvant therapy schedule will be recorded. At two months, postoperatively, urogenital, and anorectal functional evaluation will be completed. Additionally, at 3, 6, 12 and 24 months, the patient will complete quality of life questionnaires (SF36, IIEF, IPSS, LARS). Local recurrence will be evaluated at one year.

3.16 Perioperative Treatment

A standardized perioperative treatment protocol will be applied. ERAS protocol will be, also, introduced [33]. The patient will receive antibiotic chemoprophylaxis, 60 minutes preoperatively. Additionally, mechanical and antibiotic bowel preparation will be administered the previous day. Moreover, 6 and 2 hours solid and liquid food fasting, respectively, will be applied. Nasogastric tube will be removed postoperatively and will be reinserted only in cases of ileus. A multimodal analgesia will be employed, including analgesics (paracetamol, lornoxicam), and spinal or epidural analgesia. Opioid administration will be avoided. Nausea and vomiting prophylaxis will be based on granisetron 3mg/3ml IV. Mechanical and low molecular weight heparin thromboprophylaxis (28 postoperative days) will be introduced. A zero-balance fluid approach will be employed. Fluid losses will be replenished by crystalloids (Ringer's lactate). Urinary catheter will be removed at the 3rd postoperative day. Mobilization will be initiated from the 1st postoperative day. Systematic medication and per-os feeding will be started upon recovery of bowel function.

3.17 Study Group

All participating members have years of experience in their field and have, therefore, completed the learning curve for the required techniques. Data collection and recording will be carried out by an independent, third party, researcher.

3.18 Trial

The study will be conducted in the Department of Surgery of University Hospital of Larissa in collaboration with the Gastroenterology Department of University Hospital of Larissa and the Urology Department of General Hospital of Larissa. Patient data will be recorded both in the patient charts and in an electronic database. The required laboratory examinations will be defrayed by the patient insurance funds.

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