

タイトル	Pain intensity measurement after gynecological laparoscopic surgery using the Pain Vision(TM)" system for the quantitative analysis of perception and pain sensation
別タイトル	電気刺激を利用した痛み定量計測法を用いた腹腔鏡下手術の疼痛および侵襲評価
作成者(著者)	片倉, 雅文
公開者	東邦大学
発行日	2021.03.17
掲載情報	東邦大学大学院医学研究科 博士論文.
資料種別	学位論文
内容記述	主査: 高橋寛 / タイトル: Pain intensity measurement after gynecological laparoscopic surgery using the Pain Vision(TM)" system for the quantitative analysis of perception and pain sensation / 著者: Masafumi Katakura, Kentaro Nakaoka, Tomoko Taniguchi, Toshimitsu Maemura, Mineto Morita / 掲載誌: Toho Journal of Medicine / 巻号・発行年等: 7(3): 66-72, 2021 / 本文ファイル: 出版社版
著者版フラグ	ETD
報告番号	32661甲第996号
学位記番号	甲第684号
学位授与年月日	2021.03.17
学位授与機関	東邦大学
DOI	info:doi/10.14994/tohojmed.2020_012
その他資源識別子	https://mylibrary.toho-u.ac.jp/webopac/TD47749678
メタデータのURL	https://mylibrary.toho-u.ac.jp/webopac/TD18167543

Pain Intensity Measurement after Gynecological Laparoscopic Surgery Using the “Pain Vision™” System for the Quantitative Analysis of Perception and Pain Sensation

Masafumi Katakura^{1,2)*} Kentaro Nakaoka²⁾ Tomoko Taniguchi²⁾
Toshimitsu Maemura²⁾ and Mineto Morita^{1,2)}

¹⁾Department of Obstetrics and Gynecology, Toho University Graduate School of Medicine, Tokyo, Japan

²⁾Department of Obstetrics and Gynecology, Toho University Omori Medical Center, Tokyo, Japan

ABSTRACT

Introduction: Postoperative analgesia is easier if the degree of pain and factors enhancing pain with each operation can be predicted more accurately. To assess postoperative pain after gynecological laparoscopic surgery, we evaluated the extent of pain before and after treatment using the visual analogue scale (VAS) and “Pain Vision™” system, which is a quantitative analyzer of sensory perception and pain.

Methods: In total, 33 cases of laparoscopic uterine myoma enucleation (LM group) and 41 cases of laparoscopic total hysterectomy (TLH group) were assessed using the VAS and “Pain Vision™” system. The changes in the pain degree, measured using “Pain Vision™”, were evaluated over time and examined. Briefly, to measure the pain degree, an electrode is attached to the forearm, the stimulus is applied, and the current perceptual threshold and the current value of pain are registered. These values are then applied to the following equation: degree of pain = (pain response current - minimum sensing current)/minimum sensing current.

Results: The standardized regression coefficients were 0.144 for VAS and 0.229 for Pain Degree. Importantly, these values were significantly different. This analysis suggests that LM is a factor that affects the values of VAS and Pain Degree rather than TLH.

Conclusions: The postoperative pain was stronger in the LM group than in the TLH group. Based on these results, postoperative pain management should be considered separately for each surgical procedure.

Toho J Med 7 (1): 66–72, 2021

KEYWORDS: Pain Vision, post operative pain, laparoscopic surgery

Introduction

Laparoscopic surgery has become mainstream in the field of gynecology. Compared to the previously used laparotomy, it is less invasive and makes it easier for patients

to become ambulatory. However, postoperative pain management is as important as that with laparotomy in promoting bed movement.

Although laparoscopic uterine myoma enucleation (LM) and laparoscopic total hysterectomy (TLH) are widely per-

*Corresponding Author: Masafumi Katakura, 6-11-1, Omorinishi, Ota-ku, Tokyo 143-8541, Japan, tel: 03-3762-4151
e-mail: masafumi.katakura@med.toho-u.ac.jp
DOI: 10.14994/tohojmed.2020-012

Received July 3, 2020; Accepted Dec. 2, 2020
Toho Journal of Medicine 7 (1), Mar. 1, 2021.
ISSN 2189-1990, CODEN: TJMOA2

formed as gynecologic laparoscopic surgery, whether there is a difference in pain between surgical procedures has rarely been examined. It is thought that LM is a more painful procedure than TLH. A recent report compared the two surgical methods, but this was difficult to evaluate because the position of the skin incision was different for each surgical method.¹⁾ No studies have compared LM and TLH at the same site of skin incision. By comparing the pain associated with the surgical procedure itself, it will be easier to predict postoperative pain management, and more detailed care will be possible. All of our gynecological laparoscopic surgeries had the same position and size of skin incisions, which was advantageous for making pure surgical comparisons. We investigated the postoperative pain differences between the two procedures using subjective and objective pain assessment tools called the visual analogue scale (VAS) and "Pain Vision™" system.

Methods

The VAS is widely used to estimate the degree of pain, treatment effect, and postoperative pain. VAS is a subjective index that depends on the patient's personality, among other factors. It was necessary to develop a medical device that could quantify pain more easily, as it is difficult to perform an accurate assessment of when patients feel excessive pain. VAS is often used for postoperative pain evaluation. Pain control is often performed by increasing or decreasing the analgesic dosages or patient-controlled analgesia (PCA) based on subjective symptoms. However, since it is subjective, this might lead to overestimation or underestimation in postoperative management, which would interfere with the proper use of the drug, impacting the patient becoming ambulatory.

The "Pain Vision™" system (PS-2100, Nipro Corporation, Osaka, Japan) was developed and this quantitatively evaluates pain via electrical stimulation that does not induce pain by comparing the pain with the sensation of stimulus.²⁾ The principle of the "Pain Vision™" system is to compare the strength of the patient's pain with the intensity of the sensation caused by non-painful electrical stimulation and quantify the extent of the sensation corresponding to the pain according to the stimulation current value. Gynecological laparoscopic surgery is known to be less invasive and less painful than open surgery. However, women are generally sensitive to pain.³⁾ Pain assessment that is more sensitive than the VAS might improve patient quality of life.

From May 2018 to March 2019, we targeted 74 patients who underwent LM for uterine myoma and TLH for uterine myoma and adenomyosis at the Toho University Omori Medical Center. All gynecologic abdominal surgeries in our hospital are performed with four ports of the right parallel method. A camera port of 12 mm was inserted into the navel, a 5-mm port is inserted into both flanks, and a 5-mm or 12-mm port is inserted into the right groin. Although multiple surgeons were involved in this study, the main surgical procedures were the same.

All patients scheduled to receive gynecological laparoscopy with general anesthesia at our hospital were routinely managed. In the operating room, propofol at 1.5 to 2.5 mg/kg, remifentanyl at 0.5 to 1 µg/kg/min, or fentanyl at 0.5 to 1 µg/kg for induction and rocuronium at 1 mg/kg for tracheal intubation were administered. Anesthesia was maintained with remifentanyl and desflurane in 4%-6% air/oxygen to keep the bispectral index value between 30 and 60; additional rocuronium was appropriately administered to maintain the immobilization of the patients during surgery. To prevent postoperative nausea and vomiting, all patients were given dexamethasone at 6.6 mg immediately when the surgery began. Postoperative pain control was performed via intravenous PCA (IV-PCA) with 0.5 mg fentanyl with 40 ml physiological saline (in a total of 50 ml), with the following parameters: speed, 1.5 ml/h; bolus administration, 1.0 ml; lock out time, 10 minutes. As treatments, intravenous acetaminophen, diclofenac sodium sup, loxoprofen sodium per os were selected by the patient. IV-PCA could be removed on the way if the patient hoped, but the total opioid dose could not be monitored.

The resulting postoperative pain was measured over time. Measurements were taken once per day immediately after surgery (within eight hours of surgery) until the third day post-operation. The Pain Degree was measured using "Pain Vision™" and simultaneously, an evaluation of the VAS was recorded by the patients themselves. With respect to the "Pain Vision™" measurements, the electrode was attached into the inner side of the forearm, positioned at 1 cm inside the midpoint of the line connecting the center of the elbow fossa and the center of the wrist. A disposable electrode EL-BAND (Nipro Corporation, Osaka Japan) was used (Fig. 1). The forearm of the non-dominant side was used as the stimulation site, and the dominant hand was used as the switch holder. The actual measurement was performed via the connection of

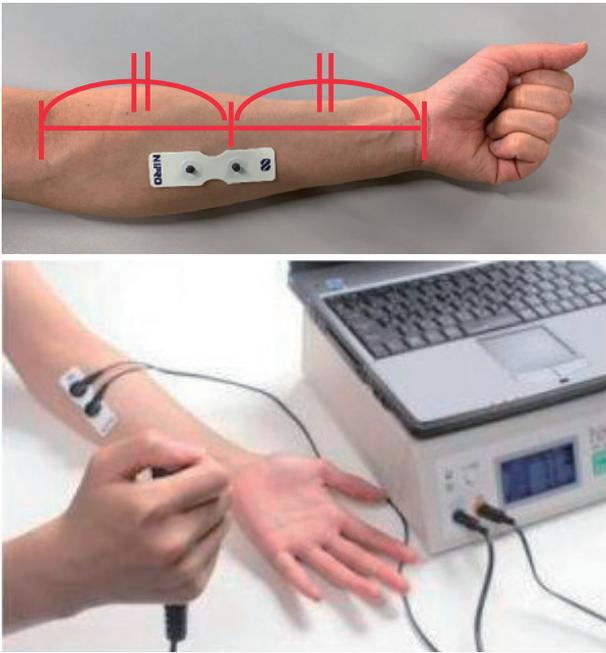


Fig. 1 Electrode mounting position (top) and measurement of Pain Degree using the Pain Vision™ system (bottom).

A disposable electrode EL-BAND is attached such that the distal electrode is located 1 cm inside the forearm, at the midpoint of the line connecting the center of the elbow fossa and the center of the wrist. The patient presses the switch when the stimulus is felt or when the stimulus is at the same level as the pain.

both the electrode and a personal computer to the “Pain Vision™” system and the launching of the relevant application (Fig. 1). The stimulus was applied using the start button and was gradually increased; the patient pressed the stop switch when the electrical stimulation was first sensed. This was repeated three times to obtain the average value of the current perception threshold. Next, the patient pressed the stop switch when the electrical stimulus and the body pain felt similar, or when the patient’s attention shifted from the pain to the electrode. This was repeated three times to obtain the average value of pain. These values were then applied to the following equation:

$$\text{Pain degree} = (\text{Pain corresponding current} - \text{Minimum sensed current}) / \text{Minimum sensed current}.$$

The VAS is a 100-mm scale, with the end point 0 for no pain and 100 for worst pain. Patients were asked to make a mark on the scale that represented their pain intensity, and pain intensity was scored by measuring the distance from the no pain end to the patient’s mark. VAS and Pain Degree were all measured by the same investigator.

For pain, we categorized the sites that could cause post-

operative pain and measured the most painful sites (intra-peritoneal, wound, urinary catheter insertion, intestinal peristalsis, seasonal ribs, shoulders, etc.). Pain Degree and VAS were measured once per day starting from immediately after surgery (POD0) to the third day after surgery. The measurement of POD0 was performed during the period from immediately after returning home to eight hours after surgery, the measurement of POD1 was performed at 24 ± 12 hours after surgery, the measurement of POD2 was performed at 48 ± 12 hours after surgery, and the measurement of POD3 was performed at 72 ± 12 hours after surgery.

In Table 2, the results are presented as the median [first quartile-third quartile]. For statistical analysis, the Mann-Whitney *U*-test was used for comparisons between the surgical procedures; $P < 0.05$ was considered significant. Moreover, Table 3 shows the results of a multiple regression analysis to predict the postoperative pain based on LM and on the postoperative time. The LM group was set to 1 and the TLH group was set to 0 as dummy variables.

This study was approved by the Ethics Committee of Toho University Omori Medical Center (approval number: M17216, approval date: January 31, 2018), and the objective and method of the study, its safety, and other parameters were fully explained to all target cases in writing.

Results

The study was carried out with the consent of the patients. The flowchart of participant recruitment is shown in Fig. 2. The characteristics of the study population are summarized in Table 1. Thirty-three patients in the LM group had a median age of 38 years, a median pregnancy history of 0, and a delivery history of 0. Overall, 100% of the group was finally diagnosed with uterine fibroids. In the TLH group, the median age of 41 patients was 46 years, the median pregnancy history was 1, the delivery history was 0, and the final pathological diagnosis in seven cases (16%) was uterine fibroids, whereas that in 37 cases (84%) was uterine adenomyosis. There was one case in the LM group and three cases in the TLH group with a history of skin disease (atopic dermatitis). Skin diseases might affect measurements by “Pain Vision™”. Therefore, these were excluded from the analysis. Table 2 shows the surgical results of the LM group with 33 patients and the TLH group with 41 patients. There was no significant difference in the surgical operating time between the two groups. The blood loss in the LM group was significantly

Table 1 Demographic and clinical characteristics

Characteristic	LM	TLH
No. of women	33	41
Age (years)	38 [34–40]	46 [43–47]
Gravidity	0 [0–1]	1 [2–2]
Parity	0 [0–0]	0 [0–2]
Diagnosis	Myoma 33 (100%)	Myoma 7 (16%) Adenomyosis 34 (84%)
BMI (kg/m ²)	21.92 [20.20–23.31]	21.50 [19.72–25.80]

Results are listed as the median [first to third quartiles]. Past medical history and diagnosis listed as (%). LM, laparoscopic uterine myoma enucleation; TLH, laparoscopic total hysterectomy; BMI, body mass index.

Table 2 Surgical outcomes

Characteristic	LM	TLH	p value
No. of cases	33	41	
Operative time (min)	85 [77–113]	99 [85–121]	0.178
Blood loss (ml)	100 [0–200]	20 [0–70]	0.007 *
Specimen weight (g)	198 [76–360]	338 [195–580]	0.019 *

Results are listed as the median [first to third quartiles]. The Mann-Whitney U test was used for statistical analysis. *: p<0.05. LM, laparoscopic uterine myoma enucleation; TLH, laparoscopic total hysterectomy.

Table 3 Postoperative outcomes

Variable	VAS				Pain Degree			
	Unstandardized regression coefficients	Standard error	Standardized regression coefficients	95% CI for Unstandardized regression coefficients	Unstandardized regression coefficients	Standard error	Standardized regression coefficients	95% CI for Unstandardized regression coefficients
LM	5.473	1.994	0.144 *	1.547 to 9.399	68.136	16.951	0.229 **	34.765 to 101.507
Post operation time	-0.357	0.039	-0.477 **	-0.434 to -0.279	-1.424	0.333	-0.244 **	-2.080 to -0.767
R ²	0.248				0.112			

Multiple regression analysis was used for the statistical analysis. *p=0.006, **p<0.001. LM, laparoscopic uterine myoma enucleation; VAS, visual analogue scale.

higher than that in the TLH group. The specimen weight was significantly higher in the TLH group than in the LM group.

Table 3 shows the effect of LM on postoperative pain compared to that with TLH. Postoperative pain was analyzed by VAS and Pain Degree. Because of VAS is a ratio of 0 to 100 and pain degree is a continuous variable, the standardized regression coefficient was used to compare them. There was a significant difference in $p < 0.05$. The

standardized regression coefficients were 0.144 for VAS and 0.229 for Pain Degree, which were significantly different. This analysis suggests that LM is a factor that affects the values of VAS and Pain Degree rather than TLH. In addition, the postoperative pain decreased with time after the operation.

Discussion

Both VAS and Pain Degree showed a significant differ-

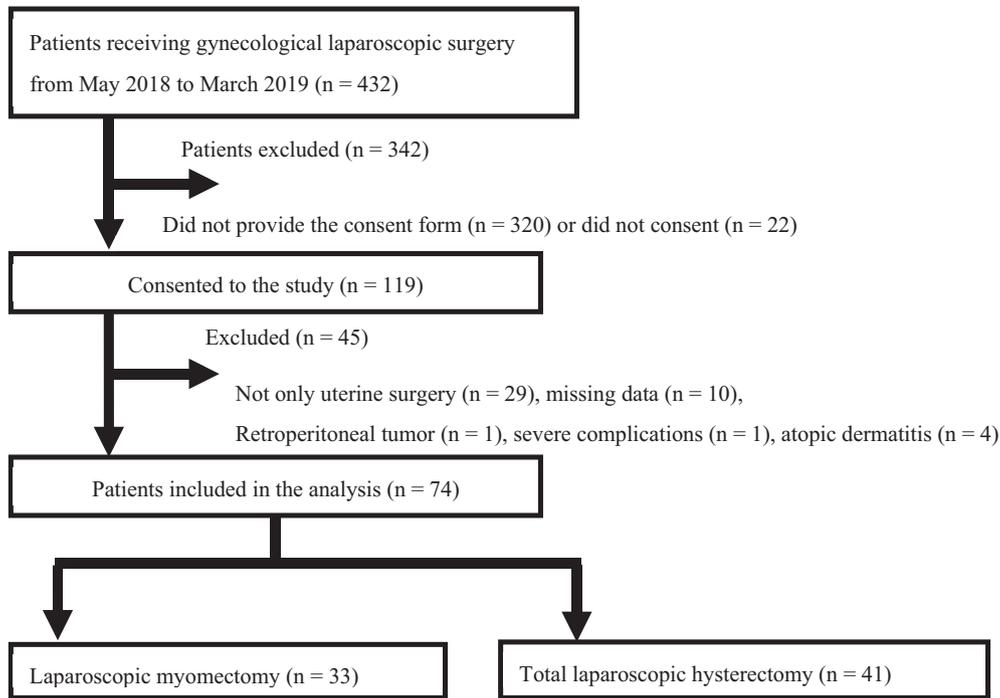


Fig. 2 Flowchart of participant recruitment in the trial

ence in postoperative pain between LM and TLH groups. Unlike previous studies, here, the site and size of the skin incision were the same for each surgical procedure, and the pain associated with each LM and TLH surgical procedure was simply compared. Similar to previous studies, the results showed that LM was associated with stronger postoperative pain, suggesting that the results were not due to differences in skin incisions. Postoperative uterine ischemia and contraction were thought to be the cause of pain in LM, but TLH was considered less painful because of the lack of a uterus. Based on the results of this study, it is predicted that LM will be more painful in advance, and thus, we considered the administration of continuous analgesics after surgery. It is expected that this will lead to custom-made pain management strategies after surgery.

Where in our experience, there are many cases in which patients report severe post-operative pain, and the pain-killer is administered at appropriate times, generally laparoscopic surgery is considered less invasive with mild post-operative pain compared to open surgery. In recent years, IV-PCA has been introduced to try to alleviate post-operative pain. In previous studies, comparisons were made between epidural anesthesia and IV-PCA for postoperative analgesia in gynecologic laparoscopic surgery, peripheral nerve block and epidural PCA in TLH, intravenous acetaminophen and intravenous NSAIDs, and fen-

tanyl and oxycodone in IV-PCA.⁴⁻⁷⁾ There might also be differences in post-surgical pain due to differences in surgical procedures and surgical contents. According to a questionnaire method, laparoscopic myomectomy was reported to be more painful than laparoscopic hysterectomy.⁸⁾ While there was also a report indicating that the risk of postoperative pain in gynecological laparoscopic surgery is increased, in addition, an examination of predictors of acute postoperative pain after gynecological laparoscopy showed that laparoscopic ectopic gestation surgery could be a postoperative pain factor and that dysmenorrhea was severe regardless of the surgical procedure.⁹⁾ We confirmed the difference in postoperative pain depending on the surgical method, quantified the degree of pain, and conducted a study to connect this with customized pain relief treatment. VAS is a subjective pain assessment method. It is affected by changes in mental status, environmental changes, and patient characteristics. In contrast, very few studies have been conducted using "Pain Vision™". In studies on the correlations among the VAS, McGill Pain Questionnaire (MPQ), and Pain Degree, some reports suggest that Pain Degree is correlated with VAS and some suggest that Pain Degree is correlated with the MPQ; other reports suggest that the degree of pain does not correlate with the VAS, which might be due to the number of cases, pain site, and clinical course.^{14,15)} Some re-

ports also showed that Pain Degree can be used to evaluate pain more sensitively than VAS.¹²⁾

“Pain Vision™” has been used to evaluate pain during the removal of wound dressings, the index of pain improvement before and after herpetic pain treatment, lower back pain, the therapeutic effect of acupuncture for lower back pain, vascular pain, and chemotherapy-induced peripheral neuropathy. It is also suggested that this system might be a good tool for evaluating pain.^{8,13-19)} In recent years, “Pain Vision™” has been used to evaluate postoperative pain and has been examined in orthopedic, respiratory, and gastrointestinal fields.¹⁶⁻¹⁸⁾ In this study, there were cases where VAS was high, but Pain Degree was not high. This suggests that VAS might be affected by subjective factors. However, Pain Degree is not a completely objective index. Because it is difficult to eliminate subjectivity, and it might be difficult to match the stimulation current depending on the pain site and the nature of the pain, there were a few cases where the pain felt by the patient was improved but Pain Degree had increased. Thus, some practice or habituation could be required to adapt the stimulation current.

In this study, all patients were treated with fentanyl-containing IV-PCA, and patients could use PCA when they wanted. In addition, the drug was also used without any restrictions for pain relief. Overall, the postoperative pain was higher in the LM group than in the TLH group. Pain degree had a higher score indicating more pain than VAS. Both somatic pain and visceral pain are mediated by A δ fibers and C fibers. The electric current utilized by the “Pain Vision™” system stimulates A δ fibers, but not C fibers. Therefore, the “Pain Vision™” system might not be able to assess the overall intensity of postoperative pain.

This study did have limitations such as subjectivity, difficulty in pain correspondence, possibility of inaccuracy in cases with skin disorders, and difficulties matching the pain with the stimulation current. Results suggest that postoperative pain management should be considered separately for each surgical procedure.

Acknowledgements: We would like to thank Editage (www.editage.com) for English language editing.

Author Contributions: MK, KN, TT, TM, and MM treated the patients and collected the clinical data. MK, KN, TT, TM, and MM interpreted the data and co-wrote the paper. All authors read and approved the final manuscript.

Conflicts of interest: None declared.

References

- 1) Shimazu H, Seno S, Kato S, Kobashi H, Akimoto M. Development of a quantitative measurement method for the magnitude of pain using painless electrical stimulation and its evaluation using experimental pain. *Trans Jpn Soc Med Biol Eng.* 2005; 43: 117-23.
- 2) Kalkman JC, Visser K, Moen J, Bonsel JG, Grobbee ED, Moons MKG. Preoperative prediction of severe postoperative pain. *Pain.* 2003; 105: 415-23.
- 3) Nielsen PR, Nørgaard L, Rasmussen LS, Kehlet H. Prediction of post-operative pain by an electrical pain stimulus. *Acta Anaesthesiol Scand.* 2007; 51: 582-6.
- 4) Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain.* 2001; 90: 261-9.
- 5) Hsu YW, Somma J, Hung YC, Tsai PS, Yang CH, Chen CC. Predicting postoperative pain by preoperative pressure pain assessment. *Anesthesiology.* 2005; 103: 613-8.
- 6) Abrishami A, Chan J, Chung F, Wong J. Preoperative pain sensitivity and its correlation with postoperative pain and analgesic consumption: A qualitative systematic review. *Anesthesiology.* 2011; 114: 445-57.
- 7) Ip HYV, Abrishami A, Peng PWH, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. *Anesthesiology.* 2009; 111: 657-77.
- 8) Matsuoka T, Yoshida Y, Aisu N, Yamada T, Mogi A, Komono A, et al. Evaluation of vascular pain in patients with colorectal cancer receiving peripheral venous chemotherapy with or without oxaliplatin. *Sci Rep.* 2019; 9: 1819.
- 9) Satoru K, Kuroda S, Nishizaki M, Matsusaki T, Mitsunashi T, Kuwada K, et al. Randomized controlled trial of epidural versus patient-controlled intravenous analgesia for postoperative pain control after laparoscopic gastrectomy. *Acta Med Okayama.* 2018; 72: 95-8.
- 10) Yamamoto Y, Kamiya C, Masaki K, Mizoguchi M, Nomoto M, Shinjo K, et al. Selection of postoperative analgesics in gynecological laparoscopic surgery - Comparison of intravenous acetaminophen and non-steroidal anti-inflammatory drugs. *J Tokai Soc Meet Gynecol Obstet Endosc.* 2018; 6: 42-6.
- 11) Park JH, Lee C, Shin Y, An JH, Ban JS, Lee JH. Comparison of oxycodone and fentanyl for postoperative patient-controlled analgesia after laparoscopic gynecological surgery. *Korean J Anesthesiol.* 2015; 68: 153-8.
- 12) Jinushi M, Kitade M, Kikuchi I, Kumakiri J, Kuroda K, Takeda S. Study on pain after laparoscopic surgery. *Jpn J Gynecol Obstet Endosc.* 2014; 30: 218.
- 13) Joo J, Moon HK, Moon YE. Identification of predictors for acute postoperative pain after gynecological laparoscopy (STROBE-compliant article). *Med.* 2019; 98: e17621.
- 14) Maekawa N, Morimoto M, Uchida T, Umeda T, Koga Y. Can we evaluate pain with Pain Vision®, a device for quantitative analysis of perception and pain?: A feasibility study of pain in Herpes Zoster patients. *J Jpn Soc Clin Anesth.* 2009; 29: 824-8.
- 15) Kim J, Lee KS, Kong SW, Kim T, Kim MJ, Park SB, et al. Correlations between electrically quantified pain degree subjectively assessed visual analogue scale, and the McGill pain questionnaire: A pilot study. *Ann Rehabil Med.* 2014; 38: 665-72.
- 16) Matsumura H, Imai R, Gondo M, Watanabe K. Evaluation of pain

- intensity measurement during the removal of wound dressing material using “the PainVision™ system” for quantitative analysis of perception and pain sensation in healthy subjects. *Int Wound J.* 2012; 9: 451-5.
- 17) Ohtori S, Kawaguchi H, Takebayashi T, Orita S, Inoue G, Yamauchi K, et al. PainVision apparatus is effective for assessing low back pain. *Asian Spine J.* 2014; 8: 793-8.
 - 18) Yoshida Y, Satoh A, Yamada T, Aisu N, Matsuoka T, Kogane-marumaru T, et al. The relationship between evaluation methods for chemotherapy-induced peripheral neuropathy. *Sci Rep.* 2019; 9: 20361.
 - 19) Lee HJ, Seo JC, Kwak MA, Park SH, Min BM, Cho MS, et al. Acupuncture for low back pain due to spondylolisthesis: Study protocol for a randomized controlled pilot trial. *Trials.* 2014; 15: 105.
 - 20) Hiraki M, Takemasa I, Uemura M, Haraguchi N, Nishimura J, Hata T, et al. Evaluation of invasiveness in single-site laparoscopic colectomy, using “the PainVision™ system” for quantitative analysis of pain sensation. *Surg Endosc.* 2014; 28: 3216-23.
 - 21) Watanabe SN, Imai K, Kimura T, Saito Y, Takashima S, Matsuzaki I, et al. Effect of lidocaine cream analgesia for chest drain tube removal after video-assisted thoracoscopic surgery for lung cancer: a randomized clinical trial. *Reg Anesth Pain Med.* 2020; 45: 16-21.
 - 22) Mifune Y, Inui A, Nagura I, Sakata R, Muto T, Harada Y, et al. Application of pain quantitative analysis device for assessment of postoperative pain after arthroscopic rotator cuff repair. *Open Orthop J.* 2015; 9: 89-93.
 - 23) Inaoka N, Shiojima S, Hanaoka M, Terada S, Adachi H, Shibuya S. Examination of factors reducing the frequency of postoperative shoulder pain after laparoscopic gynecological surgery. *Jpn J Gynecol Obstet Endosc.* 2018; 34: 75-9.

©Medical Society of Toho University. Toho Journal of Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).