Klinični pomen obsežno termično poškodovanih robov stožca po LLETZ

The clinical relevance of severe thermal artefacts in specimens after LLETZ

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Izvleček

Namen: *Pri zdravljenju ploščatocelične intraepitelijske lezije (PIL) materničnega vratu je odstranitev transformacijske cone v lokalni anesteziji z diatermično zanko (ang. LLETZ) skoraj nadomestila klasično konizacijo s skalpelom. Po LLETZ je lahko prisotna termična okvara vzorca, ki je lahko tako obsežna, da preprečuje histopatološko interpretacijo in oceno radikalnosti postopka. V literaturi je trenutno malo podatkov o prevalenci obsežnih termičnih poškodb po LLETZ in njihovi klinični pomembnosti glede potrebe po ponovni operaciji.*

Metode: *V retrospektivno raziskavo smo vključili 314 zaporednih bolnic, ki so bile v letu 2016 zdravljene na naši kliniki zaradi PIL, in sicer z LLETZ ali*

Abstract

Purpose: *Large loop excision of the transformation zone (LLETZ) under local anaesthesia has almost replaced cold knife conisation in the treatment of cervical squamous intraepithelial dysplasia (SIL). Thermal artefacts in specimens after LLETZ may be so severe, that they prevent histopathological interpretation and evaluation of the radicality of the procedure. There are limited data regarding the prevalence of severe thermal artefacts after LLETZ and their clinical relevance regarding the need for reoperation.*

Methods: *In this retrospective study, we included 314 consecutive patients who were treated with LLETZ or cold knife conisation for cervical SIL in 2016*

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klasično konizacijo. Primarni cilj raziskave je bil ugotoviti pojavnost obsežnih termičnih poškodb robov po LLETZ in vpliv na ponovitev bolezni ali potrebo po ponovni operaciji. Sekundarni cilj raziskave je bil ugotoviti pojavnost pooperativnih in kratkoročnih zapletov.

Rezultati: *Zaradi PIL smo operirali 314 bolnic. V 95,2 % primerov smo naredili LLETZ, od teh smo v 89,3 % posegov opravili v lokalni anesteziji. Ponovno operacijo smo morali izvesti v 3,8 % primerov. Pozitivni ali obsežno termično poškodovani robovi so bili prisotni v 20,4 % primerov. V 10,7 % primerov so bili termični artefakti po LLETZ tako obsežni, da jih ni bilo mogoče natančno histopatološko interpretirati, vendar je v tej skupini le ena od bolnic potrebovala ponovno operacijo. Zaradi patološkega izcedka ali krvavitve je bilo v pooperativnem obdobju potrebno obravnavati 4,7 % oz. 6,7 % bolnic.*

Zaključek: *Čeprav je imelo približno 10 % bolnic po LLETZ–u termično obsežno poškodovane robove, so le 3 % bolnic potrebovale ponovno operacijo. Po naših izkušnjah obsežno termično poškodovani robovi niso povezani z večjo potrebo po ponovni operaciji. Za odločitev o ponovni operaciji je tako pomembnejše redno sledenje, in sicer s citološkimi brisi, testiranjem na prisotnost visokoriziničnih HPV in kolposkopijo z biopsijo.*

at our clinic. The primary outcome of the study was to determine the prevalence of severely damaged surgical margins after LLETZ and if these thermal artefacts can predict residual disease or the need for reoperation. The secondary outcome was the prevalence of postoperative and short–term complications.

Results: *Three hundred and fourteen women underwent surgery for cervical SIL. In 95.2% of cases, we performed LLETZ, and 89.3% of women had this procedure under local anaesthesia. The reoperation rate was 3.8%. Positive or inconclusive margins were present in 20.4% of specimens. In 10.7% of all LLETZ cases, thermal artefacts were so severe that they interfered with histopathological interpretation. However, only one of these patients needed reoperation. Postoperative vaginal discharge and mild bleeding requiring therapeutic intervention occurred in 4.7% and 6.7% of cases, respectively.*

Conclusion: *Although approximately 10% of patients had severe thermally damaged margins after LLETZ, only 3% required reoperation. In our experience, severely damaged margins were not associated with higher reoperation rate. On the other hand, a carefully planned follow–up visit with cytology, human papillomavirus (HPV) testing and colposcopy with biopsy after the procedure is of utmost importance in the evaluation of residual disease..*

INTRODUCTION

Cervical cancer is the fourth most common cancer and the fourth most common cause of death due to cancer in women worldwide (1). Following the introduction of screening programmes, the incidence and mortality of cervical cancer have decreased. During screening, the Papanicolaou (Pap) smear and HPV tests are used. In the case of an abnormal screening test, colposcopy with biopsy is indicated (2) and in the case of high–grade squamous (HSIL) or glandular lesions, treatment is indicated. Either ablation or excision of

the transformation zone where the lesion is located is performed. However, ablation techniques are rarely used since they have only a few advantages compared to excisional techniques (3). The excisional procedures performed are cold knife conisation or large loop excision of the transformation zone (LLETZ). These procedures provide a diagnostic specimen, which is a significant advantage. Although cold knife conisation usually removes a larger volume of tissue than LLETZ (4) and avoids thermal damage of the cone margins, LLETZ under local anaesthesia has almost completely replaced cold knife conisation, which is traditionally performed under general anaesthesia. Several studies have shown that patients with negative margins after excision are at significantly lower risk of residual disease (5–7). Although studies have evaluated thermal artefacts of margins after LLETZ (8–12), the data on the effect of severe thermal artefacts which interfere with pathological interpretation and their impact on the need for reoperation are scarce. Therefore, the aim of the present study was to determine the prevalence of severe thermally damaged surgical margins after LLETZ and to evaluate if these thermal artefacts can predict residual disease or the need for reoperation.

METHODS

This was a single–centre retrospective study, which was conducted at the Department for Gynaecological Oncology and Breast Oncology, University Medical Centre (UMC) Maribor, Slovenia. The primary outcome of the study was determination of the prevalence of severely damaged surgical margins after LLETZ and if these thermal artefacts can predict residual disease or the need for reoperation. The secondary outcome was the occurrence of immediate postoperative and short–term complications, which were assessed at an unscheduled visit at our outpatient clinic.

All consecutive patients who were surgically treated for squamous (SIL) or glandular cervical intraepithelial lesions at our clinic from January 1st to December 31st, 2016 were included in the study. Patients were treated with one of two excisional techniques, either LLETZ or cold knife conisation. Cold knife conisation was used in cases with large lesions, which could not be sufficiently excised with an electrical loop. The indication for treatment (high–grade glandular lesions, persistent low–grade squamous or glandular lesions or mismatch between high–grade cytological and low–grade histological preoperative diagnosis with unsatisfactory colposcopy with transformation zone 2 or 3) was based on Slovenian national guidelines (13). LLETZ was performed in an outpatient setting under local anaesthesia with 0.5–1% lidocaine or under general anaesthesia in patients who did not consent to local anaesthesia. The procedure was performed using KLS Martin Maxium® with loop devices ranging from 10 mm to 20 mm in size, using a monopolar current with the cut frequency set to 100–150 W. The wound surface was then coagulated with the coagulation frequency set from 60 W to 80 W. Cold knife conisation was performed under general anaesthesia. After the procedure, histopathological analysis of the surgical specimen (conus) was performed by a team of experienced pathologists from the same hospital. Short–term postoperative complications (30 days after procedure) were determined. Following our national guidelines, colposcopy with Pap smear with or without biopsy was performed at the first follow–up 6 months after the procedure. In the case of high–grade dysplasia, either squamous or glandular, reoperation was performed. We obtained written informed consent forms from the patients who agreed to the use of their medical records for research purposes, quality control and retrospective statistical analysis of the data. Statistical analysis was performed using SPSS Statistics software 25.0 (IBM, United States of America). Descriptive statistics were calculated based on the patients' characteristics. The Chi–square test, Fisher's exact test, Mann Whitney and Kappa tests were used to compare data between groups. Statistical significance was set at a p–value <0.05.

RESULTS

In 2016, we surgically treated 314 patients with SIL or glandular cervical intraepithelial lesions. Of these patients, 95.2% (299/314) underwent LLETZ and 4.8% (15/314) underwent cold knife conisation. The median

age of the patients was 38±12.5 years (range 20–77 years). LLETZ under local anaesthesia was performed in 89.3% (267/299) of patients, while the remaining 10.7% (32/299) had general anaesthesia. All cold knife conisations were performed under general anaesthesia. After the procedure, histopathological analysis of the cone was performed, and the excision margins were assessed. The excision margins were negative in 79.6% (250/314) of cases, positive in 9.9% (31/314) of cases and inconclusive in 10.5% (33/314) of cases. Of the 33 specimens with inconclusive margins, 32 were after LLETZ (10.7% (32/299) of all patients after LLETZ) in which severe thermal artefacts of the specimen interfered with histopathological interpretation. The remaining one specimen with inconclusive margins was after cold knife conisation due to severe fragmentation of the specimen.

Altogether, 3.8% (12/314) of patients underwent reoperation, 10 after LLETZ and 2 after cold knife conisation. When analysing patients who were reoperated after LLETZ, 21.4% (6/28) of them were reoperated after showing positive margins, 1.3% (3/239) after showing negative margins and only 3.1% (1/32) after severe thermal artefacts in the primary specimens (Table 1). In the group of patients who underwent reoperation after cold knife conisation, one patient had positive margins, and another had a severely fragmented specimen. Two patients were reoperated immediately after the first LLETZ due to cervical carcinoma, and the others were reoperated six months after the primary procedure when a scheduled follow-up visit was performed and histological HSIL was confirmed.

In the postoperative period, the most frequently observed complications were vaginal bleeding and discharge. Overall, complications occurred in 8.3% (26/314) of cases. Isolated bleeding occurred in 3.5% (11/314) of cases, isolated discharge in 1.6% (5/314) of cases, and both symptoms in 3.2% (10/314) of cases (Table 1). With regard to the impact of the type of procedure on the occurrence of postoperative complications, we discovered that the type of

Table 1. *Comparison between LLETZ and classical conisation regarding number of procedures, type of anaesthesia, margin status, postoperative complications and the need for reoperation.*

		LLETZ N (%)	Conisation N (%)	Total N (%)
Variable		299 (95.2)	15 (4.8)	314 (100)
Anaesthesia	Local	267 (89.3)	0 (0)	267 (85.0)
	General	32 (10.7)	15 (100)	47 (15.0)
Margin status	Negative	239 (79.9)	11 (73.3)	250 (79.6)
	Positive	28 (9.4)	3 (20.0)	31 (9.9)
	Inconclusive	32 (10.7)	1 (6.7)	33 (10.5)
Postoperative complications	Isolated vaginal bleeding	10 (3.3)	1 (6.7)	11 (3.5)
	Isolated vaginal discharge	5 (1.7)	0 (0)	5 (1.6)
	Vaginal bleeding and discharge	9 (3.0)	1 (6.7)	10 (3.2)
	Total	24 (8.0)	2 (13.3)	26 (8.3)
Reoperation		10 (3.3)	2 (13.3)	12 (3.8)

procedure (LLETZ or cold knife conisation) did not significantly affect vaginal bleeding (6.4% vs 13.3%, respectively, p=0.265) or vaginal discharge (4.7% vs. 6.7%, respectively, p=0.528). However, we found that bleeding occurred more often in younger (U=3033; p=0.914) and discharge (U=1994; p=0.469) in older patients, but the impact was not statistically significant.

DISCUSSION

In this retrospective study, 10.7% of patients after LLETZ had severe thermal artefacts in the specimen that interfered with histopathological evaluation. However, only one of these patients (3.1%) required reoperation. In comparison, in patients with positive margins after LLETZ, the reoperation rate was 21.4%, and in patients with negative margins, the reoperation rate was 1.3%. The overall reoperation rate was 3.8% and most patients (58.3%) who needed reoperation had positive margins after the primary procedure.

Since its introduction in 1989, LLETZ has become the most commonly used method for the surgical treatment of cervical high–grade squamous or glandular cervical lesions. The idea behind LLETZ was to combine the advantages of local destructive techniques with those of classic cold knife conisation (14). One of the biggest concerns when performing LLETZ is inadequate histopathological interpretation due to thermal injury of the tissue that occurs due to the use of electricity which simultaneously cuts and cauterizes the lesion. In 1994, Messing et al. divided thermal injury of the tissue into three grades (slight, moderate and severe). Slight thermal injury was defined as a thermal alteration that allowed histological evaluation to be performed without any difficulty. Moderate thermal injury was defined as thermal alterations that resulted in some difficulty in correctly interpreting the severity of the neoplasia and in evaluating the actual involvement of the resection margins. Severe thermal injury was defined as intense thermal damage in which histopathological evaluation of the specimen was not possible (15). Although a slight degree of thermal injury can be seen in almost all LLETZ specimens (8), the prevalence of severe thermal injury is much lower, up to 26%, depending on the loop size, speed of cutting, electrical energy, tissue conductivity and perhaps even the surgeon's experience (8,15,16).

Many studies have emphasized the importance of surgical margins after surgical treatment of cervical lesions. The presence of high–grade dysplasia in the margin (endocervical, ectocervical and lateral) is associated with a higher risk of disease relapse and the need for additional surgical treatment in the future. Therefore, the aim of the surgeon should be to excise the lesion completely (5,7,17), but in the case of severe thermal artefacts, we suggest that follow–up visits are performed in an experienced colposcopy centre as colposcopy with biopsy is crucial in determining the success of treatment. In addition, there is known inter– and intra–observer variability in colposcopy, cytology and pathology, causing different predictive values of the methods (18–20). Nevertheless, our experience shows that patients with artefacts due to severe thermal damage are not at increased risk for reoperation. We hypothesise that this might be due to complete thermal destruction of the cells around the cut surface of the cone. Therefore, even if the precancerous cells were located close to the surgical margin, the thermal energy of the loop would destroy them.

Surgical treatment is associated with the possibility of postoperative complications. In our study, the overall incidence of postoperative complications was low (4.7–6.7%) and there were no statistically significant differences in postoperative vaginal bleeding or discharge between the types of surgical procedure. Patients who developed bleeding were younger and patients who presented with discharge were older; however, there were no statistically significant differences between the groups. Some studies have shown that classical conisation is associated with a higher incidence of postoperative bleeding and vaginal discharge than LLETZ (5–15% vs. 0–8% and 0.2–6.8% vs. 0–2%, respectively) (10,21–27), but others have not confirmed these results (28). Other possible short–term side effects reported in the literature such as pelvic pain and stenosis of the cervical canal (29) were not observed in our group of patients. Also, long–term side effects or complications such as preterm labor were not an endpoint of this study; therefore, they were not included in the analysis.

The major limitations of this study are its retrospective nature and the relatively small number of included

patients. Moreover, the patients were not equally distributed between the groups and the number of postoperative complications was low. These drawbacks restricted the statistical analysis, and major conclusions should be drawn with caution.

Although every tenth patient after LLETZ had severe thermal artefacts that prevented histopathological interpretation, only 3% of them required reoperation. In our experience, severely damaged margins were not associated with higher reoperation rate; therefore, a carefully planned follow-up visit with colposcopy and cytology 6 months after the procedure is of utmost importance in the evaluation of residual disease.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest. Some of the results were presented as a poster at the 26th European Congress of the European Board & College of Obstetrics and Gynaecology in Paris, France, March 8–10, 2018.

REFERENCES

1. Stewart BW, Wild CP. World cancer report 2014. 632 p.
2. Cantor SB, Cardenas-Turanzas M, Cox DD, Atkinson EN, Nogueras-Gonzalez GM, Beck JR, et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. Obstet Gynec 2008; 111(1): 7–14.
3. Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO, Keep SL. Surgery for cervical intraepithelial neoplasia. Cochrane database Syst Rev 2010(6); Cd001318.
4. Phadnis SV, Atilade A, Young MP, Evans H, Walker PG. The volume perspective: a comparison of two excisional treatments for cervical intraepithelial neoplasia (laser versus LLETZ). BJOG : an international journal of obstetrics and gynaecology. 2010; 117(5): 615–9.
5. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncol. 2007; 8(11): 985–93.
6. Maluf PJ, Adad SJ, Murta EF. Outcome after conization for cervical intraepithelial neoplasia grade III: relation with surgical margins, extension to the crypts and mitoses. Tumori 2004; 90(5): 473–7.
7. Park JY, Lee SM, Yoo CW, Kang S, Park SY, Seo SS. Risk factors predicting residual disease in subsequent hysterectomy following conization for cervical intraepithelial neoplasia (CIN) III and microinvasive cervical cancer. Gynecol Oncol 2007; 107(1): 39–44.
8. Garcia Ramos AM, Garcia Ramos ES, Dos Reis HL, de Rezende RB. Quality evaluation of cone biopsy specimens obtained by large loop excision of the transformation zone. J Clin Med Res 2015; 7(4): 220–4.
9. Fischer NR, Alexandarian D, Gagliardi S, Oglesby J, Scribner D, Asuncion C, et al. Evaluation of the cone biopsy excisor compared with the large loop for electrosurgical excision of cervical lesions. Primary care update for Ob/Gyns 1998; 5(4): 161–2.
10. Takač I, Fokter N, Dovnik A, Arko D. A prospective study of the correlation between infection of the uterine cervix and secondary bleeding after large loop excision of the transformation zone (LLETZ). Acta Med Biotech 2011; 4(2): 45–50.
11. Waxman AG, Chelmow D, Darragh TM, Lawson H, Moscicki AB. Revised terminology for cervical his-

topathology and its implications for management of high–grade squamous intraepithelial lesions of the cervix. Obstet Gynec 2012; 120(6): 1465–71.
12. Khunamornpong S, Raungrongmorakot K, Siriaunkgul S. Loop electrosurgical excision procedure (LEEP) at Maharaj Nakorn Chiang Mai Hospital: problems in pathologic evaluation. J Med Assoc Thai 2001; 84(4): 507–14.
13. Uršič Vrščaj M. Smernice za celostno obravnavo žensk s predrakavimi spremembami materničnega vratu. In: Ljubljana OI, editor. Ljubljana 2011.
14. Prendiville W, Cullimore J, Norman S. Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. BJOG: An International Journal of Obstetrics & Gynaecology. 1989; 96(9): 1054–60.
15. Messing MJ, Otken L, King LA, Gallup DG. Large loop excision of the transformation zone (LLETZ): a pathologic evaluation. Gynecol Oncol 1994; 52(2): 207–11.
16. Sparić R, Tinelli A, Guido M, Stefanović R, Babović I, Kesić V. The role of surgeons' colposcopic experience in obtaining adequate samples by large loop excision of the transformation zone in women of reproductive age. Geburtsh Frauenh 2016; 76(12): 1339.
17. Manchanda R, Baldwin P, Crawford R, Vowler S, Moseley R, Latimer J, et al. Effect of margin status on cervical intraepithelial neoplasia recurrence following LLETZ in women over 50 years. BJOG: An International Journal of Obstetrics & Gynaecology 2008; 115(10): 1238–42.
18. Bornstein J, Bentley J, Bosze P, Girardi F, Haefner H, Menton M, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynec 2012; 120(1): 166–72.
19. Underwood M, Arbyn M, Parry–Smith W, De Bellis–Ayres S, Todd R, Redman CW, et al. Accuracy of colposcopy–directed punch biopsies: a systematic review and meta–analysis. BJOG : an international journal of obstetrics and gynaecology 2012; 119(11): 1293–301.
20. Nanda K, McCrory D, Myers E, Bastian L, Hasselblad V, Hickey J, et al. Accuracy of the Papanicolaou Test in Screening for and Follow–up of Cervical Cytologic Abnormalities: A Systematic Review. J Low Genit Tract Dis 2001; 5(1): 60.
21. Gilbert L, Saunders NJ, Stringer R, Sharp F. Hemostasis and cold knife cone biopsy: a prospective randomized trial comparing a suture versus non–suture technique. Obstet Gynec 1989; 74(4): 640–3.
22. Oyesanya OA, Amerasinghe C, Manning EA. A comparison between loop diathermy conization and cold–knife conization for management of cervical dysplasia associated with unsatisfactory colposcopy. Gynecol Oncol 1993; 50(1): 84–8.
23. Keijser KG, Kenemans P, van der Zanden PH, Schijf CP, Vooijs GP, Rolland R. Diathermy loop excision in the management of cervical intraepithelial neoplasia: diagnosis and treatment in one procedure. Am J Obstet Gynec 1992; 166(4): 1281–7.
24. Gavrić Lovrec V, Erlah T, Dobnik S, Takač I. The influence of smoking on the frequency and characteristics of complications following large loop excision of the transformation zone (LLETZ). Acta Med Biotech 2019; 12(1): 40–6.
25. Arko D, Dovnik A, Fokter N, Takac I. The role of genital pathogens in morbidity following diathermy loop excision of the transformation zone of the uterine cervix. Int J Gynaecol Obstet 2012; 117(1): 27–9.
26. Arko D, Dovnik A, Fokter N, Takač I. A prospective study of the correlation between infection of the uterine cervix and secondary bleeding after large loop excision of the transformation zone (LLETZ). Acta Med Biotech 2011; 4(2): 45–50.
27. Arko D, Takac I. A prospective study of the correlation between Chlamydia trachomatis infection and secondary bleeding following large loop excision of the transformation zone (LLETZ). Wien Klin Wochenschr 2001; 113 Suppl 3: 11–3.
28. Jiang YM, Chen CX, Li L. Meta–analysis of cold–knife conization versus loop electrosurgical excision procedure for cervical intraepithelial neoplasia. OncoTargets Ther 2016; 9: 3907–15.
29. Kyrgiou M, Mitra A, Arbyn M, Stasinou SM, Martin–Hirsch P, Bennett P, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta–analysis. BMJ (Clinical research ed) 2014; 349: g6192.