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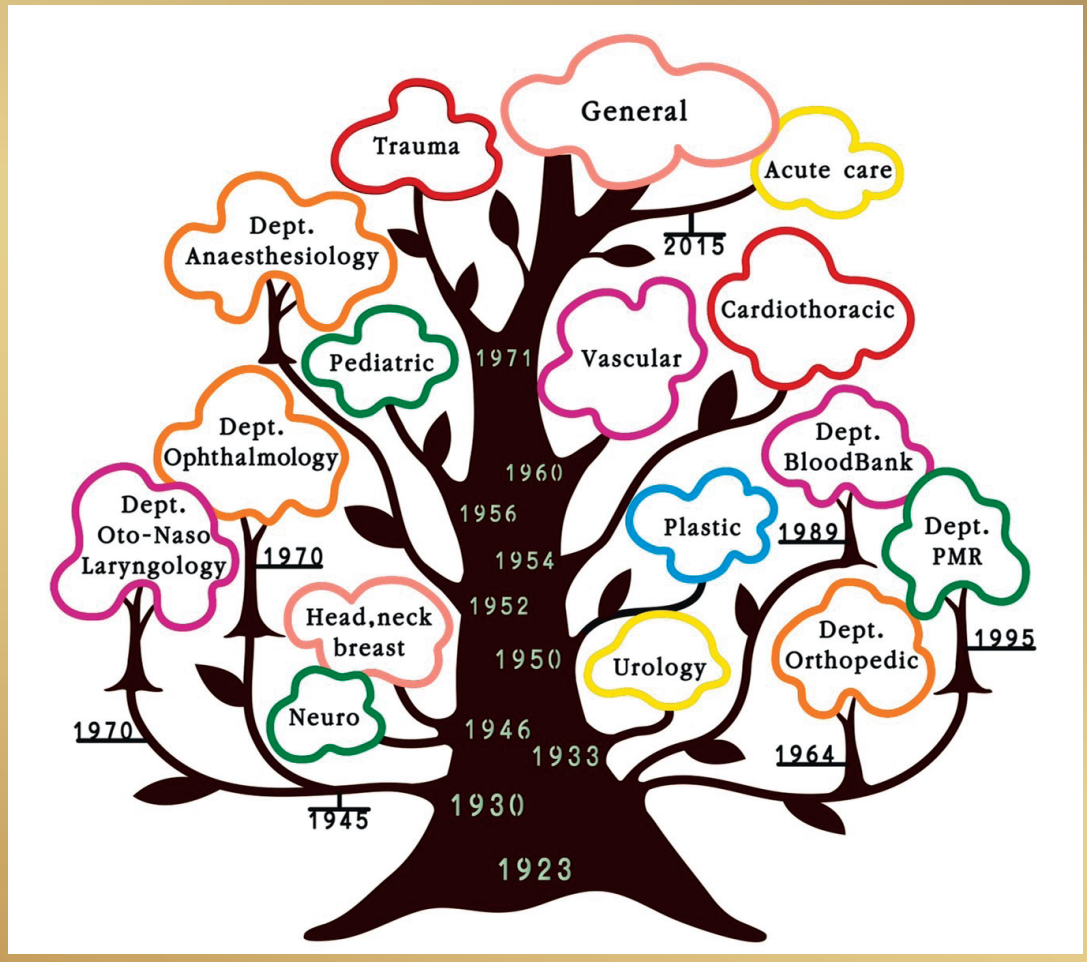

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Pure Flat Epithelial Atypia of the Breast on Core Needle Biopsy: No Need for Surgical Excision

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ABSTRACT

Objective: From previous data, pure flat epithelial atypia (FEA) of the breast demonstrated on core needle biopsy (CNB) was related to malignant upgrading. However, FEA itself is not an independent factor for developing breast cancer; therefore, the necessity of subsequent surgical excision is controversial. This study aimed to evaluate the upgrade rate of FEA after surgical excision and to demonstrate the necessity of surgical excision in FEA lesions identified on CNB.

Materials and Methods: This retrospective study involved a review of the clinical features, mammographic and ultrasound findings, and pathological reports of patients with pure FEA found from CNB specimens between January 2010 to January 2019. FEA accompanied with atypical ductal hyperplasia, atypical lobular hyperplasia, ductal carcinoma in situ (DCIS), and invasive cancer (IC) in ipsilateral breast were excluded. FEA upgrade is defined as patients with in situ or invasive cancer presented in surgical excision specimens. The breast imaging results of pure FEA and FEA upgrade subsets were compared.

Results: In total, 45 pure FEA specimens were revealed from CNB; of which, 6 of the pure FEA (13.33%) did not undergo further surgical excision, however, they showed no recurrence during follow-up (median follow-up time: 2.68 years). The majority of FEA cases were detected by mammography in 39 patients (86.67%). Of the 45 patients, 32 were classified into BI-RADS 4B (71.11%), 11 as BI-RADS 4A (24.44%), and 2 as BI-RADS 4C (4.44%). One patient was upgraded to DCIS (2.7%). BI-RADS classification did not differ between upgrade FEA and non-upgrade FEA groups (p=0.49).

Conclusion: Only a 2.7% upgrade rate, omitting the surgical excision of pure FEA from CNB, was possible. Even though our study could not demonstrate a correlation between FEA upgrade and radiological findings, BIRADS 4A was less likely to carry the malignant cells. Furthermore, segmental microcalcification tended to be associated with upgraded lesions, but not significantly.

Keywords: Breast cancer; flat epithelial atypia (FEA); upgrade rate (Siriraj Med J 2021; 73: 727-731)

INTRODUCTION

In recent decades, the diagnosis of flat epithelial atypia (FEA) has been increasing. Previously, FEA was known as intraepithelial neoplasia, albeit with an unclear exact pathological description. In 2003, the World Health Organization (WHO) coined the term "flat epithelial atypia" to describe a lesion where native ductal cells are replaced by atypical columnar or cuboidal cells.[1] The incidence of upgrading to malignancy, in which atypical cells occur concomitantly with malignancy (in

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situ or invasive carcinoma) in larger specimens, after FEA has been diagnosed in core needle biopsy (CNB) specimens as varying from 0 - 42%.[2-4] Therefore, the current standard treatment for FEA after CNB is surgical excision. However, FEA itself is not an independent factor for developing breast cancer. Previous studies found no risk of breast cancer in FEA lesions after 13 years follow-up.[5,6] As a result, the necessity for subsequent surgical excision is controversial. This study aimed to evaluate the upgrading rate of FEA after surgical excision and to evaluate FEA patients identified by CNB who have the potential to avoid surgical excision.

MATERIALS AND METHODS

This study involved a retrospective analysis of medical records and was approved by the Ethics Committee of the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital (Si 482/2019). All pathological reports from CNB specimens diagnosed as FEA from January 2010 to January 2019 were reviewed. Pure FEA from core needle biopsy specimens, defined as only FEA or FEA concomitantly occurring with other non-proliferative or benign proliferative epithelial lesions, were included. All patients had mammography (MMG) and breast ultrasound (US) performed followed by core needle biopsy at Siriraj Hospital. FEA accompanied with atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), ductal carcinoma in situ (DCIS), and invasive cancer (IC) in ipsilateral breast were excluded. However, pure FEA from CNB in one breast with contralateral ADH, ALH, DCIS, and IC were included. All patients underwent excisional biopsy, otherwise in the case of patients for whom surgical excision was not performed, they needed to undergo surveillance at Siriraj Hospital.

Clinical presentation, mammographic and ultrasonographic findings, and pathological reports were collected. For core needle tissue sampling, suspicious microcalcifications were biopsied by stereotactic-guided biopsy using a 14-gauge core-biopsy needle (BARD®MAGNUM®), 14- or 9-gauge vacuum-assisted device (Eviva®, Hologic), and if a mass was targeted, ultrasound guidance with a 14-gauge needle (BARD®, MAGNUM®). The average was obtained from five cores. A radiographic clip was placed in some patients for facilitating follow-up.

Statistical analyses were performed using SPSS software version 21 (IBM SSPS, Chicago, IL). Categorical data was reported as the median with the interquartile range, mean with SD, or as a percentage. The chi-square test was used to examine the association between upgrade to malignancy, the morphology, and the distribution of the microcalcifications. Student's t-test or Mann–Whitney U-test was applied to analyze the continuous data. For the categorical data, the χ^2-test or Fisher-exact test were used to analyze for statistical significance. A p-value less than 0.05 was considered statistically significant throughout this study.

RESULTS

During January 2010 to January 2019, 45 pure FEA lesions diagnosed from CNB were identified. The baseline characteristics of the patients are described in Table 1. Of these 45 lesions, 39 were surgically removed. Six lesions (13.3%) were observed with no following surgery; however, they showed no recurrence during surveillance (median follow-up, 2.7 years; range, 29–2844 days). In this study, only one lesion was found upgraded to DCIS. The median age at diagnosis was 49 years old. Of the 45 patients, 5 (11.1%) had a history of benign breast disease at the index breast, while no-one had a family history of breast or ovarian cancer. The majority of FEA were detected by mammography (39 lesions; 86.7%); whereas, 6 lesions were detected by ultrasonography. When classifying according to BI-RADS classification (Breast Imaging Reporting and Data System, established by the American College of Radiology), 11 lesions were categorized into BI-RADS 4a (24.4%), 32 into BI-RADS 4b (71.1%), and only 2 into BI-RADS 4c (4.4%). All 45 lesions were biopsied; 73.3% stereotactic-guided, 13.3% vacuum assisted, and 13.3% by US-guided (Table 1).

In cases in which surgical excision was done, FEA from CNBs were found as pure FEA in the final surgical specimens in 26 of 39 patients (66.7%) and coexisted with either ADH, IDC, or DCIS in 13 patients (33.3%) (Table 2). Of these latter 13 patients, 1 patient was upgraded to DCIS (2.6% of total pure FEA from CNB), while no-one was associated with invasive cancer, and 1 patient had FEA with ALH (2.6%); meanwhile, 11 patients had FEA accompanied with ADH (28.2%): 8 found with ADH and 3 found with ADH, ALH, or LCIS.

Regarding the radiological findings of the 26 patients whose final surgical specimens had confirmed FEA, 8 of the 26 patients were BIRADS 4a (30.8%), 17 were BIRADS 4b (65.4%), and 1 was BIRADS 4c (3.9%). Four lesions were detected by US and 22 by MMG. The mammographic findings of pure FEA presented with microcalcification (MC) were as described. In terms of the shape, 19 were amorphous, 2 punctate, and 1 round. In terms of the distribution, there were 9 clusters, 8 groups, 4 regional, and 1 linear.

There were 12 lesions for which the final pathological report from the surgical excisional specimen demonstrated

TABLE 1. Baseline characteristics of pure FEA from CNB patients.

Characters	CNB pure FEA (n = 45)
Age (years)	
Range	37–61
Median	49.0
Detected lesions	
Microcalcification	39
Mass	5
Microcalcification with mass	1
BIRADS	
1–3	0
4a	11
4b	32
4c	2
5	0
Target lesion sampling	
Microcalcification	39
Stereotactic	33
Vacuum assisted	6
Mass	
USG-guided	6
Residual calcification	
Yes	16
No	18
Unknown	5
Surgery after FEA identified from CNB	
Yes	39
No	6
Histology of excision specimens	
Pure FEA	26
FEA with AH	12
FEA with cancer	1

Abbreviations: AH: atypical hyperplasia, CNB: core needle biopsy, FEA: flat epithelial atypia

TABLE 2. Radiographic findings according to the final histological results.

Group Factor	Total n = 39, (%)	Pure FEA n = 26, (%)	FEA with AH n = 12, (%)	FEA with DCIS n = 1, (%)	P-value
Detection methods					
MMG	35	22	12	1	
US	4	4	0	0	
BI-RADS					
4A	9	8 (30.8)	1 (8.3)	0	0.49
4B	28	17 (65.4)	10 (83.3)	1 (100)	
4C	2	1 (3.9)	1 (8.3)	0	

FEA combined with high-risk benign breast lesion. Of these 12 lesions, 10 were BIRADS 4b (83.3%), 1 was BIRADS 4a (8.3%), and 1 was BIRADS4c (8.3%). In terms of the shape of the microcalcifications in these 12 lesions, 10 were amorphous, 1 was fine linear, and 1 was punctuate. Interestingly, 1 patient whose final surgical excision specimen showed DCIS was categorized into BIRADS 4b with segmental amorphous microcalcification. When comparing the BIRADS classifications, no difference was observed between the pure and combined FEA subgroups ($p = 0.49$).

DISCUSSION

Overall, 1 lesion in our study was upgraded to DCIS (2.6%) and none of the lesions were invasive carcinoma. In addition, breast cancer did not occur whether omitting the surgical group or following surgery in the group without the upgrading. Despite the risk of subsequent breast cancer of FEA being unclear, just as in previous studies, this could not be proven conclusively[5,7], but FEA itself tended to not increase the risk of subsequent cancer. Said et al. found no increasing long-term breast cancer events when FEA was found concomitantly with either atypical hyperplasia (AH) or proliferative lesions (PL): [AH + FEA 4.74 vs. AH 4.23; $p = 0.59$] and [PL + FEA 2.04 vs. PL 1.90; $p = 0.76$], respectively.[6] In the case of pure FEA after surgical excision, de Mascarel et al. also found that none of the pure FEA patients in their study had breast cancer during 10-year follow-ups.[8] The findings from our study were similar in terms of the rarity of events following upgrading to malignancy in FEA lesions diagnosed on CNB.

In practice, pure FEA from CNB should be followed by surgical removal. This relies on previous evidence, which demonstrated a 10-40% combination of FEA with other malignant lesions (either *in situ* or invasive carcinoma) from CNB specimens.[2-4,9] However, when emphasizing cancer upgrading (DCIS or invasive cancer), the possibility of FEA accompanying these malignant cells is low (7.5%) compared to its co-incidence with other high-risk lesions (18.6%).[2] When vacuum-assisted core needle biopsy (VCNB) was first introduced, the rate of upgrading decreased dramatically. Recent investigations using VCNB reported decreasing histologic upstaging at 0 - 3%.[10,11] However, even our practices did not routinely use VCNB in all microcalcification-detected cases, and our upgrading rate was only 2.6%. The necessity of surgical excision, therefore, is controversial.

Despite the low incidence of malignant upgrading, the rate of combining ADH was high (30.7%). In addition, our study could not demonstrate the correlation between FEA upgrading and radiologic findings. Even though most patients presented with suspicious microcalcifications detected by mammography and were classified into BIRADS 4b, the study population was too small to specify the significance of the imaging classification to discriminate whether the lesion was pure or mixed FEA. In the case of mammographic abnormalities, amorphous microcalcifications were more commonly identified in 30 of 39 specimens (76.9%) than other shapes and the majority were distributed as clusters. In 1 lesion with DCIS upgrading, the patient presented with segmental amorphous microcalcification, which was the only case where the microcalcification was distributed as a segmental shape. Likewise, previous studies failed to identify the specific radiographic characters for FEA upstaging[3,12], which tended to be clustered or segmental amorphous microcalcifications.[3,13] Although, no distinctive breast imaging was noted, FEA diagnosed as BIRADS 4a was less likely to be upgraded, and occurred in only one of 9 patients (11.1%), meanwhile, FEA also occurred with BIRADS 4b (11 of 28; 39.3%) or 4c (1 of 2; 50%); therefore, BIRADS classification was not a good independent predictor for selecting patients to observe instead of performing surgery. Among one of several studies, Alencherry et al. recently reported that one of the independent risk factors to upstaging was a history of cancer in individuals or first-degree relatives[13,14], but no patients in our cohort had a family history of breast cancer.

However, there were some limitations in our study to note. As the pathological definition of FEA has only recently been introduced in the past few decades, there may have been interobserver variabilities of the interpretation among pathologists and it might have been reported as columnar cell change in some cases, thus causing a smaller number to be included in the study population, especially as we could not review all the slide specimens. Another shortcoming, because of the higher cost of vacuum-assisted devices, is that in our hospital, core needle biopsy with a 14-gauge needle rather than VCNB is the most practised technique, which might be less accurate.

CONCLUSION

Flat epithelial atypia is a marker of carrying a high risk lesion rather than for upgrading to breast cancer. Even though the histological finding may show atypical cells, the risk of subsequent breast cancer is very low compared to ADH. Surgical excision may be omitted particularly in cases of pure FEA from core needle biopsy.

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Sacral Neuromodulation in the Treatment of Non-Neurogenic Female Lower Urinary Tract Dysfunction; First Case-series and Systematic Review of Literature

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ABSTRACT

Objective: To demonstrate which types of non-neurogenic female lower urinary tract dysfunction (LUTD) respond to sacral neuromodulation (SNM) after the failure of all non-invasive treatments.

Materials and Methods: Female LUTD performed SNM between 2017 and 2019 were retrospectively reviewed. A case with anatomical or neurological abnormalities were excluded by thorough physical examination and investigations. The specific type of LUTD, including midurethral obstruction (MUO), was diagnosed by videourodynamics (VUDS). Clinical diagnoses, including idiopathic urinary retention (IUR), voiding dysfunction (VD) and refractory overactive bladder (OAB), were used instead of VUDS diagnosis when the result was normal or inconclusive. The International Prostate Symptom Score (IPSS) and Overactive Bladder Symptom Score (OABSS) in Thai version were used to compare between pre and post-treatment. Responder was defined as an IPSS and/or OABSS decreased more than 50% from baseline.

Results: Total 21 cases were performed SNM. The average age was 49.6 (24–80) years. The average pre-treatment IPSS and OABSS were 23.4 and 6.4 as well as average post-treatment IPSS and OABSS were 13.7 and 3.8. Only 9 out of 21 cases (42.9%) showed improvement after SNM. The responders included 7 out of 11 MUO (63.6%), 1 out of 4 IUR (25.0%), and 1 out of 3 OAB (33.3%). None of the VD cases responded to SNM.

Conclusions: SNM is another option for female patients with LUTD who have failed to respond to conservative treatments. After completely excluding anatomical and neurological abnormalities, the types of LUTD having a chance to respond to SNM are MUO, IUR, and OAB.

Keywords: Lower urinary tract dysfunction, Female, Sacral neuromodulation (Siriraj Med J 2021; 73: 732-737)

Abbreviation

LUTD : Lower urinary tract dysfunction
SNM : Sacral neuromodulation
VUDS : Videourodynamics
BOO : Bladder outlet obstruction
MUO : Midurethral obstruction
DU : Detrusor underactivity
IUR : Idiopathic urinary retention
VD : Voiding dysfunction
OAB : Overactive bladder

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INTRODUCTION

Lower urinary dysfunction (LUTD) is a functional problem that mainly causes lower urinary symptoms in women and usually affects their quality of life. Functional abnormalities in each patient may consist of bladder and/or outlet dysfunction. Because LUTD is a dynamic abnormality and changes over time, the appropriate management for LUTD should be conservative treatment and/or medication. However, lower urinary tract symptoms may not properly be alleviated by non-invasive treatment; while invasive surgery will rarely be considered due to the risk of a permanent change of function. Neuromodulation, a treatment using electrical stimulation directly to the nerve in order to modulate the reflexes that influence the bladder, sphincters, bowel, and pelvic floor[1] to restore normal lower urinary tract function, has been widely accepted for treating LUTD and is considered as a non-invasive procedure. Nowadays, there are many neuromodulation procedures that have been used for treating LUTD, but the most popular one is sacral neuromodulation (SNM), which has supported from many scientific studies. The US FDA has approved the use of InterStim™ or SNM for the treatment of urgency-frequency syndrome, urinary urge incontinence, and non-obstructive urinary retention.[2] In Thailand, neuromodulation has been used in many neurological conditions but there has never had a study of neuromodulation for treating LUTD. Consequently, this study aims to demonstrate our experience and to provide the LUTD characteristics of patients who have a chance to obtain a benefit from SNM.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 21 female patients with non-neurogenic LUTD who were performed SNM between 2017 and 2019 in our hospital. This study was approved by our institute IRB, number 714/2562(IRB2)

Patient selection

The inclusion criteria were female patients with LUTD who had not responded or had an unsatisfactory response to all conservative treatments for more than 6 months. All cases would like to try SNM after counselling and understanding the risks and benefits of procedure. Further, physical and neurological examination must reveal no significant anatomical or neurological abnormality that could probably be a cause of the LUTD. All the cases had videourodynamics (VUDS) performed followed by the International Continence Society (ICS) recommendation[3] in order to diagnose a type of functional abnormality and to get a clear urodynamic diagnosis before SNM was performed. Because surface electromyography during VUDS was unreliable, the result was not considered as a part of diagnosis and fluoroscopic imaging was used instead of it. In cases of normal or inconclusive result due to situational inability to void, clinical diagnosis was used for the grouping instead of urodynamic diagnosis.

Definitions

According to ICS terminology 2010, the definition of characteristics of LUTD consist of an overactive bladder (OAB), defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology; voiding dysfunction (VD), defined as an abnormally slow and/or incomplete micturition; detrusor underactivity (DU), defined as a detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span; and bladder outlet obstruction (BOO), defined as a reduced urine flow rate and/or presence of a raised post-void residual urine and an increased detrusor pressure.[4] The urodynamic criteria for the diagnosis of female BOO were described in Blaivas's study.[5] In this group, the point of obstruction could be demonstrated by fluoroscopic examination on VUDS so that specific term, including midurethral obstruction (MUO), was used instead of BOO. Urethral stricture must be excluded by cystourethroscopy in all BOO cases. In cases of normal or inconclusive VUDS, the clinical diagnosis consisted of voiding dysfunction (VD), defined as a maximal urine flow rate equal to or less than 12 ml/sec with or without post-void residual urine; idiopathic urinary retention (IUR), defined as a past or current inability to void; and refractory overactive bladder (OAB), defined as OAB which had failed to respond to conservative treatment and medications or led to intolerable adverse events. Responders were defined as being cured or showed an improvement after SNM.

Measurement

The validated questionnaires in the Thai language, including the International Prostate Symptom Score (IPSS)[6] and Overactive Bladder Symptom Score (OABSS)[7], were used as a symptom measurement tool. Cure was defined as an IPSS and/or OABSS improvement of more than 80% from baseline, while improvement was defined as an IPSS and/or OABSS improvement of between 50% and 80% from baseline within 7-30 days after implantation and the last follow-up for the response cases. Responder was defined as a case who was cure or improvement after SNM.

Procedure

Sacral neuromodulation (SNM) is usually performed in two stages: a test phase and a phase with implantation of an implantable pulse generator (IPG) by using the InterStim II® system (Medtronic). The test phase utilized two techniques: temporary lead implantation, called percutaneous nerve evaluation (PNE), and permanent tined lead implantation, composed of four leads and a hook. The full SNM system consisted of a permanent tined lead and IPG. Lead implantation was performed in the prone position, in a well-prepared sterile field and under local anesthesia with light sedation. Fluoroscopic guidance was used to identify the 3rd sacral foramen in two-dimensions, in the anteroposterior and lateral views. A 20-gauge needle in the set of SNM was used to make a puncture at 2 cm cephalad to the 3rd sacral foramen in the anteroposterior view and at the 45°–60° axis in the lateral view. The needle was passed through the foramen and stopped at the anterior surface. The proximal end of the needle was connected to an external pacemaker and then electrical stimulation was given. The proper position of the needle was defined by the patient reporting feeling a tickling sensation at the perianal area, anus, and/or vagina, called a sensory response and demonstrating anal contraction, called a motor response. If the selected site did not demonstrate any response, the procedure would be repeated at the contralateral site in the same step. The needle stylet was then removed. Either a temporary lead or permanent lead was inserted via the needle and placed in a proper position by checking the sensory and motor responses. For PNE, the lead was fixed directly at the puncture site using a transparent medical dressing. For the permanent lead, a subcutaneous tunnel was created by a trocar with a plastic tube from the puncture site to the subcutaneous pocket at the right buttock and the lead was connected to an extended wire to directly connect to an external pacemaker in order to prevent contamination. Due to the easy displacement of the PNE lead, some cases reporting no response might repeat either PNE or permanent tined lead implantation if the patient agrees. During the test phase, the external pacemaker was used as an electrical generator and the implanted patient could adjust the intensity of the electrical stimulation by monitoring their feeling in the perianal area, anus, and vagina. If the feeling was too much, electrical stimulation could be reduced by remote control. For evaluation, if a patient reported symptoms improvement of more than 50% from baseline by IPSS and OABSS, full SNM system implantation would be performed within 1-4 weeks. Because of the high cost of full SNM system implantation, PNE was considered as a first step in all cases who had unsuccessful VUDS or where there were doubts about the benefit of SNM. All cases of full SNM system implantation were supported by the high cost treatment project of our hospital foundation.

Statistics

The results were presented using descriptive statistics as a frequency and percentage for categorical data, as well as average for continuous data.

RESULTS

In total, 21 cases of female LUTD who had SNM performed. The average age was 49.6 (24 – 80) years. The types of LUTD consisted of MUO 11 cases, IUR 4 cases, VD 3 cases, and OAB 3 cases. MUO and VD cases were treated by non-invasive management including behavioral therapy, pelvic floor muscle rehabilitation and oral medications. IUR cases were initially treated by indwelling catheter and then performed clean intermittent catheterization. OAB cases were treated step by step including first - single oral bladder relaxant, second - combination of oral high dose bladder relaxant and last - 100 unit of intradetrusor botulinum toxin A injection. The average pre-treatment IPSS and OABSS were 23.4 and 6.4 as well as the average post-treatment IPSS and OABSS were 13.7 and 3.8. (Table 1) Only 9 out of 21 cases (42.9%) were cured or improved after SNM. The responders included 7 out of 11 MUO (63.6%), 1 out of 4 IUR (25.0%), and 1 out of 3 OAB (33.3%). None of the VD cases responded to SNM. Twelve of 21 cases had complete VUDS successfully performed. (Table 2) Only 8 out of 9 responders had fully implanted SNM and the average follow-up was 15.4 (4.4 – 32.4) months, while the average IPSS and OABSS were 8.4 and 2.7, respectively. One case decided not to continue with SNM because of an awareness of the foreign body and fear of the long-term consequences (Table 3). In total, 6 out of 8 cases reported and considered themselves cured. No adverse events were reported in all cases.

DISCUSSION

Female LUTD without anatomical and neurologic abnormality is a challenging condition. Importantly, it is not a life-threatening condition but always affects the patient's quality of life. Because of the dynamic changes that can occur, the most appropriate treatment, including conservative and medical treatment, should be reversible over time, meaning that invasive surgery is not an ideal option. However, while most patients are properly treated by conservative and medical treatment, some patients may not achieve their goal. SNM is another treatment

TABLE 1. Comparison between average pre- and post-treatment IPSS and OABSS in each type of LUTD.

Type of LUTD		No.	IPSS		OABSS	
			Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
MUO	Responder	7	23.7	5.4	6.0	1.9
	Non-responder	4	18.3	15.0	3.5	2.6
IUR	Responder	1	34.0	6.0	6.0	3.0
	Non-responder	3	27.3	22.7	4.0	2.7
DV	Responder	0	-	-	-	-
	Non-responder	3	25.3	23.3	8.3	8.3
OAB	Responder	1	15.0	0	9.0	0
	Non-responder	2	15.5	15.5	11.0	11.0

TABLE 2. Case number, diagnosis and videourodynamics parameters in each case.

Case no.	Age	Dx	Group	VV	PVR	Free uroflow	Urodynamic parameters		
						Qmax	Catheter Qmax	Pdet at Qmax	Fluoroscopic findings
1	35	MUO	Responder	178	0	12.9	-	-	Mid
2	54	MUO	Responder	115	155	-	4.2	80	Mid
3	41	MUO	Non-responder	67	0	13.8	4.8	51.5	Mid
4	54	MUO	Responder	40	205	-	2.1	57.5	Mid
5	68	MUO	Responder	81	154	25	4.3	23	Mid
6	53	MUO	Responder	376	0	16	16.4	26.5	Mid
7	53	MUO	Non-responder	144	0	-	10.3	61.2	Mid
8	38	MUO	Non-responder	210	0	18.8	-	-	Mid
9	24	MUO	Responder	65	0	-	8.8	24	Mid
10	76	MUO	Responder	80	96	-	5	25	Mid
11	80	MUO	Non-responder	274	63	11	8.8	37.2	Mid
12	42	IUR	Non-responder	199	202	11.6	-	-	-
13	45	IUR	Non-responder	161	80	6.9	-	-	-
14	31	IUR	Non-responder	126	150	10.2	-	-	-
15	36	IUR	Responder	70	600	4	-	-	-
16	38	VD	Non-responder	592	0	12	-	-	-
17	34	VD	Non-responder	233	200	10	-	-	-
18	65	VD	Non-responder	256	0	11.5	-	-	-
19	76	OAB	Responder	491	0	-	21.9	17.1	No BOO
20	41	OAB	Non-responder	420	0	-	25.5	30	No BOO
21	59	OAB	Non-responder	180	0	-	24.2	28.2	No BOO

Abbreviations: Dx : diagnosis, VV : voided volume (ml), PVR : post-void residual urine (ml), Qmax : maximal urine flow rate (ml/sec), Pdet@Qmax : detrusor pressure at maximal urine flow rate (cmH2O), Mid : midurethral obstruction, BOO : bladder outlet obstruction

TABLE 3. Comparison between pre- and post-treatment IPSS and OABSS in responder group at the last follow up.

Case no.	Age (year)	Diagnosis	Follow time (month)	IPSS Pre-treatment	IPSS Post-treatment	OABSS Pre-treatment	OABSS Post-treatment	Status
1	35	MUO	32.4	31	0	3	0	Cure
2	54	MUO	21.2	40	1	15	1	Cure
4	54	MUO	7.1	22	11	6	2	Improvement
5	68	MUO	13.0	20	8	4	3	Improvement
6	53	MUO	12.7	15	0	2	2	Cure
9	24	MUO	-	19	-	11	-	Not perform
10	76	MUO	4.4	19	1	1	1	Cure
15	36	IUR	7.3	34	4	6	2	Cure
19	76	rOAB	25.2	15	5	9	4	Cure

option and is appropriate for LUTD. In our study, we categorized female LUTD into 4 types based on firstly urodynamic and lastly clinical diagnosis, including MUO, IUR, DV, and OAB.

For female BOO, common locations of obstruction are the bladder neck and midurethral. Bladder neck obstruction is usually treated by an alpha-adrenergic antagonist or transurethral incision bladder neck. On the other hand, most MUO cases are usually treated and respond to SNM. Soumendra et al. reported a 10-year experience of SNM for females with urinary retention secondary to external urethral sphincter overactivity or Fowler's syndrome. The overall success was 72% and the results revealed that females with normal urethral sphincter activity had worse outcomes than those with an abnormal urethral sphincter activity.[8] In our study, female BOO was diagnosed by VUDS according to the criteria in Blaivas's study[5] and we found 11 cases were MUO. In total, 7 out of 11 (63.6%) MUO cases responded to SNM and the success rate was comparable.

In our study, both IUR and DV were clinical diagnoses because of inconclusive VUDS result, such that they might be detrusor acontractility (DAC), DU, BOO, or combined abnormalities. Rademakers et al. performed a study in 18 men with DU, defined as a measurement value less than the 25th percentile in the linear interpolation of a Maastricht–Hannover nomogram, and reported that 50% of the cases responded to SNM.[9] Chan et al. performed a study in 50 women and 19 men with DU, defined as having a bladder contractility index (BCI = Pdet at Qmax + 5Qmax) of less than 100, and reported that 51% of cases had a favorable response to the trial phase, defined by at least a 50% improvement in symptoms, PVR, and voided volume bladder diary. Interestingly, 6 of 18 cases with detrusor acontractility, defined by an absent contractility with failure to empty and absence of EMG abnormalities, had a favorable response to the trial phase. They concluded that patients with preserved detrusor contractility were more likely to respond to SNM.[10] In our study, only one of our IUR cases successfully responded to SNM, which probably meant this patient had enough detrusor contractility or BOO.

Noblett et al. performed a study in patients with OAB, confirmed on a consecutive three-day voiding diary with a minimum of two involuntary leaking episodes in 72 hours and/or ≥ 8 voids per day, where success at 12 months was defined as a ≥50% improvement in average leaks/day or ≥50% improvement in voids/day or a return to normal voiding frequency (<8 voids/day). The responder rate was 85% in overall OAB symptoms. Only 37% of OAB cases with UUI had complete continence.[11] In our study, 1 of our 3 OAB cases gained continence and was cured.

A key strength of our study study is that we tried to identify dysfunctional causes in each case by VUDS in order to make it clear which type of LUTD would benefit from SNM. However, urodynamic diagnosis should be a key tool to predict SNM response, as VUDS could not be successfully performed for most cases. Because the

test is in an unnatural setting, we even tried to perform it in a similar way to mimic a patient's lower urinary tract function. Importantly, strict urodynamic criteria for diagnosing female BOO and DU are inconclusive and difficult to draw conclusions, so that the SNM results of many studies highly depend on patient selection. Lastly, the limitations of this study to note are its small sample size and retrospective design, which prompt the need for further research.

CONCLUSION

SNM is another option for female patients with non-neurogenic LUTD who have failed to respond to all conservative treatments. In our study, after completely excluding anatomical abnormalities, the type of LUTD having the highest chance to respond to SNM was found to be midurethral obstruction (MUO). For idiopathic urinary retention (IUR) and refractory overactive bladder (OAB), only one-third of cases responded. No voiding dysfunction (VD) cases responded to SNM. This information may help urologists to better select patients for SNM.

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Temporal Bone Landmarks of the Transverse-sigmoid Sinus Junction: An Anatomical Study in Dried Human Skulls

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ABSTRACT

Objective: To investigate the accuracy in localization of the anterosuperior margin of TSSJ by using the intersection point between the squamosal and parietomastoid sutures (A point) and the intersection of the squamosal suture and supramastoid crest (B point) as bony landmarks.

Materials and Methods: The A and B points were marked on the inner surface of a skull by using the transillumination technique. The anatomical relationship between the projected A point, B point, and groove of TSSJ was investigated in 60 dried Thai human skulls (120 sides).

Results: Of the 120 sides, the projected A points were located exactly on the anterosuperior margin of the TSSJ in 38 (31.7%) instances and adjacent (above and below) the anterosuperior margin in 82 (68.3%) cases. Of the 118 sides with identifiable supramastoid crests, the projected B points were located precisely on the anterosuperior margin of TSSJ in 60 (50.8%) cases and above the anterosuperior margin of the TSSJ in 57 (48.3%) cases. Hence, the projected B point was a more reliable bony landmark for localizing the anterosuperior margin of the TSSJ when compared with the projected A point (p = 0.003, OR 2.2, and 95% CI =1.3-3.8).

Conclusion: The B point is a more reliable temporal bone landmark for localization of the TSSJ than the A point. In temporal craniotomy, an initial burr hole at the B point is relatively safe and carries a very low risk of inadvertent venous sinus injury.

Keywords: Relationship; transverse-sigmoid sinus junction; squamosal suture; parietomastoid suture; supramastoid crest; temporal craniotomy; middle cranial fossa (Siriraj Med J 2021; 73: 738-743)

INTRODUCTION

In neurosurgical practice, temporal craniotomy is one of the most common surgical approaches for dealing with lesions that involve the middle cranial fossa. This procedure is also the key component for more aggressive lateral skull base approaches such as the transpetrosal approach. The posterior boundary of this approach is defined by the transverse-sigmoid sinus junction (TSSJ). In order to maximize craniotomy size and to avoid inadvertent venous sinus injury, localization of this major venous sinus is crucial during planning for craniotomy.[1-9] Although the neuronavigation system is extremely useful nowadays, it is not generally available in a resource-limited public hospital or emergency situation.[2] As a result, anatomical landmarks are still important for neurosurgeons, especially when performing initial burr hole placement.[1-9] The temporal bone is known for its complexity with various bony landmarkssuch

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as the squamosal suture, parietomastoid suture, and supramastoid crest. There has been controversy in previous anatomical studies regarding the best bony landmark of TSSJ in which the intersection between the squamosal and parietomastoid sutures and the intersection between the squamosal suture and supramastoid crest have been mentioned.[1,6-9] Both intersections have been commonly used as the bony landmark of TSSJ. Additionally, race-based differences of the skull may also affect the surgical approach and make one bony landmark suitable for one race but unreliable for another.[10-11] The authors of this study used dried human skulls to investigate the relationship between the temporal bone landmarks and TSSJ.

MATERIALS AND METHODS

One hundred twenty temporal bones from 60 dried Thai adult human skulls were evaluated in this study. The squamosal sutures, parietomastoid sutures, and supramastoid crest were identified at the outer surface of the skull. On the inner surface, the grooves of the transverse sinuses and sigmoid sinuses and TSSJ were identified. For practicality issues, if there was variation in sutures such as presence of sutural bone causing multiple sutures, the most conspicuous suture line would be used. After identifying these key structures, a point on the intersection between the squamosal and parietomastoid sutures was labeled as the "Apoint", and the intersection between the squamosal suture and supramastoid crest was determined to be the "Bpoint". Both points were then marked on the outer surface of the skull (Fig1). The A and B points were then projected onto the inner surface of the skull and traced via a transillumination technique using a laser pointer positioned perpendicular to the skull's surface (Fig 2). The projected points A and B were then evaluated according to whether they were situated on TSSJ (Fig 3). If confirmed, it would be further classified as the projected points would be positioned exactly at the anterosuperior margin or other areas of the TSSJ. Also, the relationship between the anterosuperior margin of TSSJ and projected A and B point was described and a distance between these landmarks was measured along the horizontal (X) and vertical (Y) axis.

This study was ethically approved by the Institutional Review Board (IRB) at Siriraj Hospital, Mahidol University (Si 717/2561 (Exempt)).

Statistical analysis

A statistical analysis was performed using PASW version 22.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used to investigate characteristics of the study sample, including median, range, and percentage for numerical data. Accuracy of the projected A point and B point for predicting the location of the TSSJ was analyzed using Pearson's chi-squared test. A p-value of less than 0.05 was considered statistically significant. Odds ratio (OR) and 95% confidence interval (CI) was estimated from Pearson's chi-squared test.

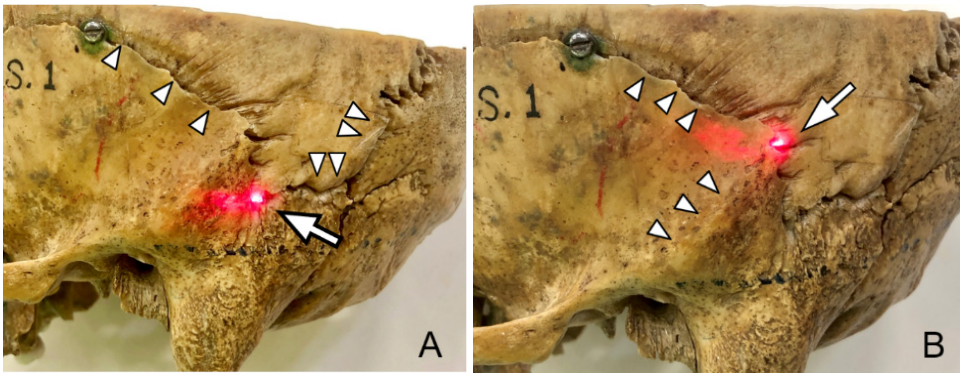

Fig 1. Key points on the outer surface of the skull. (A): "Apoint" (arrow), defined as the point of intersection between the squamosal (arrowhead) and parietomastoid sutures (double arrowheads); (B): "Bpoint" (arrow), defined as the point of intersection between squamosal suture (arrowhead) and supramastoid crest (double arrowheads); MP refers to mastoid process.

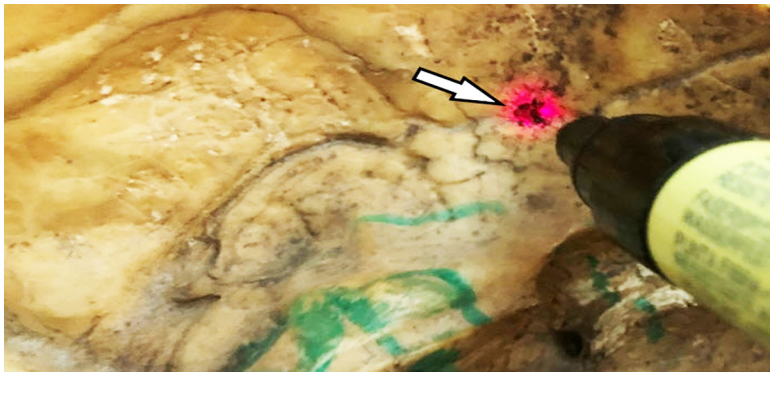

Fig 2. Transillumination technique using a laser pointer perpendicular to the outer surface of the skull and marking of the projected point (arrow) on the inner surface of the skull.

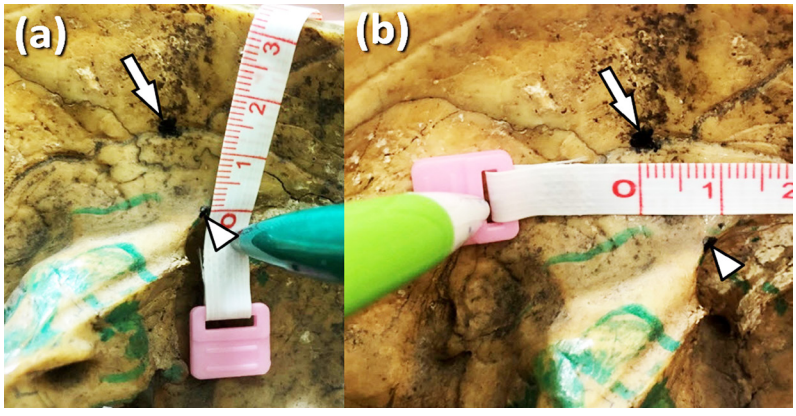

Fig 3. Measurement of distance between the projected A point (arrow) and the anterosuperior margin of TSSJ (arrowhead) in vertical (a) and horizontal (b) directions.

RESULTS

Demographic characteristics

The mean age of the skull specimens was 38 ± 11.1 years (range 18-60 years). Of the sixty skulls, 30 (50%) were male, and 29 (48.3%) were female. The remaining skull (1.7%) belonged to an unknown gender.

The relationship between the projected A point and anterosuperior margin of the TSSJ

The projected A points were located exactly on the anterosuperior margin of the TSSJ in 38 out of 120 cases (31.7%). In 82 out of 120 cases (68.3%), the projected A points were not exactly located on the sinus margin but situated adjacent (either above or below) the anterosuperior margin of the TSSJ (Fig 4A). The distance from the projected A point to the anterosuperior margin of the TSSJ ranged from -16 to 12 mm (median 0 mm) on the X-axis and -14 to 17 mm (median 0 mm) on the Y-axis.

The relationship between the projected B point and anterosuperior margin of the TSSJ

Of the 60 human skulls, one was excluded due to its unidentifiable bilateral supramastoid crest. The projected B points were located exactly on the anterosuperior margin of the TSSJ in 60 of the remaining 118 sides (50.8%). In cases where the projected B points were not exactly located on the sinus margin, almost all of the points were situated above the anterosuperior margin of the TSSJ (57 of 118 sides or 48.3%). The projected B point of the remaining one side was positioned within the TSSJ below the anterosuperior margin (Fig 4B). The distance from the projected B point to the anterosuperior margin of the TSSJ ranged from -14 to 9 mm (median 0 mm) on the X-axis and -4 to 28 mm (median 0 mm) on the Y-axis.

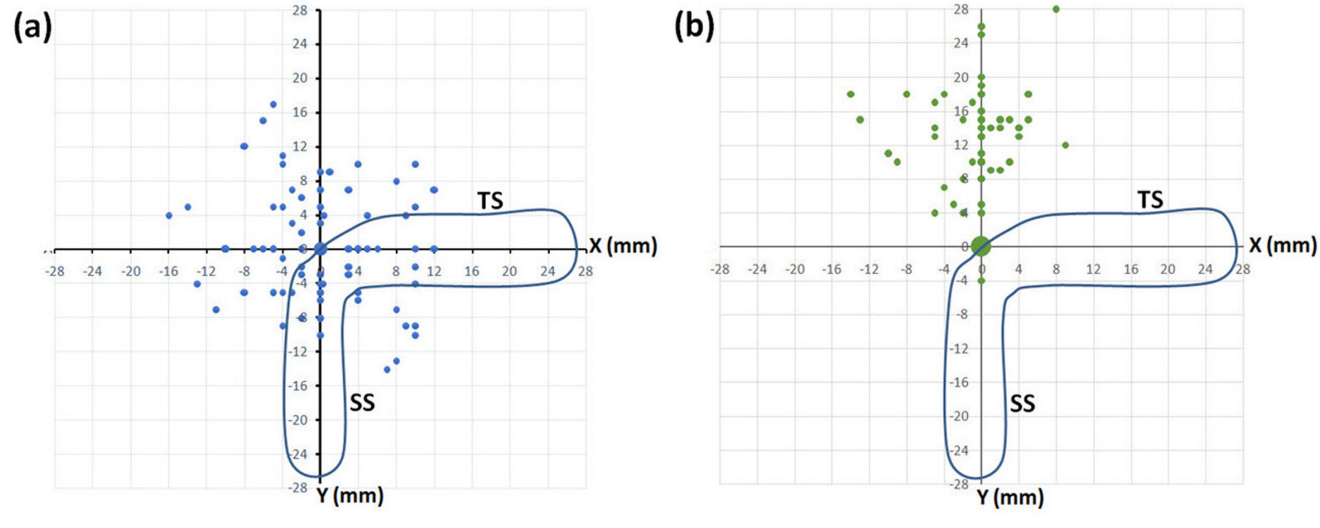

Fig 4. The distribution of the projected A (a) and B points (b) related to the location of the transverse sigmoid sinus junction (TSSJ). In both figures, the intersection between the X- and Y-axis indicate the anterosuperior margin of the TSSJ; SS, sigmoid sinus; TS, transverse sinus.

Comparison between the accuracy of the projected A and B points for predicting the location of the anterosuperior margin of the TSSJ

Sixty out of one-hundred and eighteen sides (50.8%) of the projected B points were located exactly on the anterosuperior margin of the TSSJ whereas the projected A points were located on the anterosuperior margin in 38 of 120 cases (31.7%). This difference in accuracy was statistically significant (p = 0.003, OR 2.2, and 95% CI =1.3-3.8).

Comparison between the accuracy of A and B points for predicting the location of the TSSJ (excluding the anterosuperior margin of the sinus)

The projected A points were located within the TSSJ in 21 of 120 sides (17.5%) while the projected B point was located with the TSSJ in only one out of 118 sides (0.8%). This difference of accuracy was statistically significant (p < 0.001, OR 24.8, 95% CI = 3.3-187.8).

The effect of gender on anatomical relationships

When a subgroup analysis with gender was done, the pattern of relationship between projected A points, B points and the anterosuperior margin of the TSSJ was the same as above in both genders.

Between genders, there was no significant difference in relationship between the projected A point, B point and the anterosuperior margin of the TSSJ (p=0.291 for A point, p=0.475 for B point)

In both genders, the projected B point was significantly more accurate in predicting the location of the TSSJ (excluding the anterosuperior margin of the sinus) than the A point (p < 0.001). When predicting the location of the anterosuperior margin of the TSSJ, the projected B point was significantly more accurate than the A point in females (p=0.004, OR 2.8) but not significant in males (p=0.267, OR 1.5).

DISCUSSION

In dealing with surgical lesions in the middle cranial fossa, temporal craniotomy is the key procedure. However, it is also used as the major component of more aggressive skull base approaches such as the transpetrosal approach. In order to perform an effective craniotomy, neurosurgeons should create an appropriately-sized cranial opening while avoiding injury of the adjacent major venous sinuses.[1-10] Since the posterior boundary of temporal craniotomy is determined using the position of TSSJ, precise identification of this major venous structure, especially the anterosuperior margin of the venous junction, is crucial. Moreover, despite technological advancements in the neuronavigation system, which helps facilitate safer and faster surgery[2], it is not usually available in a resource-limited public hospital or emergency situation. Therefore, anatomical bony landmarks are still essential for neurosurgeons in the initial burr hole process before beginning temporal craniotomy.

The temporal bone is one of the most complex in the human body as it is full of various anatomical landmarks, such as squamosal suture, parietomastoid suture, supramastoid crest, etc. The point of intersection between the squamosal and parietomastoid sutures (A point) and the point of intersection between the squamosal suture and supramastoid crest (B point) are commonly used as the surface landmark to help locate TSSJ.[1,6-10] However, previous anatomical and clinical studies reported heterogeneous results and no direct comparison between both the bony landmarks was studied.

Ucerler and Gosva noted that the asterion was a reliable bony landmark for TSSJ, however, when it was not exactly superficial, it was mostly inferior to TSSJ.[5] This meant that the asterion was a suitable bony landmark for posterior cranial fossa approachesbut not for temporal craniotomy, in which the location of the craniotomy is superior to TSSJ. Raza and Quinones-Hinojosa proposed a surgical technique for the extended retrosigmoid approach that includes an initial burr hole that encompasses TSSJ, however, it was slightly supratentorial.[2] Despite this, they did not mention the exact landmark of the burr hole. Ribas et al. also studied dried human skulls and found that the meeting point between the parietomastoid and squamous sutures could be easily identified and were related to the superior margin of the transverse sinus or floor of the middle cranial fossa.[1] However, this study did not mention TSSJ directly. Studies by Bozbuga et al and Day et al used an imaginary line connecting the squamosal-parietomastoid suture junction and mastoid tip to the identify sigmoid sinus trajectory but they did not directly study the relationship between this line and the TSSJ.[6-7]

Goto and his coworkers also described their technique for the safe exposure of the sigmoid sinus in presigmoid approaches. They used the intersection between the supramastoid crest and squamosal suture as a landmark for the anterior margin of TSSJ in this large case series.[9] Li et al. studied anatomical landmarks of the anterosuperior point of the TSSJ using dried human skulls. They compared the location of the squamosal-parietomastoid suture junction with their coordinate system and concluded it was more accurate in localization of the venous sinus junction.[8]

Additionally, a radiological study of cranial surface landmarks and the venous sinus was conducted by Sheng

and colleagues. They used computerized tomography angiography and found that 89% of the squamosal-parietomastoid suture junctions were located superior and anterior to TSSJ.[10] In our opinion, the use of a 3-dimensional anatomical study is more accurate than a 2-dimensional radiological study.

There are also studies showing that how the size, shape, and structure of the cranium could be different across ethnic groups.[11] These differences can be large enough to affect surgical approaches. Low et al. found that Europeans had a greater petrous angle than Chinese people and therefore they recommended a larger craniotomy size in Europeans.[12] For this reason, our study was specific to the Thai population. Duangthongpon et al. studied supramastoid crest as a surgical landmark for temporal craniotomy and found that the supramastoid crest is easy to identify and safe from injury. However, they did not compare it with other available landmarks.[13]

In our study, three major anatomical landmarks, including the squamosal and parietomastoid sutures, and supramastoid crest, were consistently identifiable in almost all specimens. It was only in one specimen (0.8%) that the supramastoid crest could not be identified bilaterally. Comparing the accuracy of the projected A and B points in predicting the location of the anterosuperior margin of the TSSJ, B point was relatively more accurate when it came to bony landmarks (p = 0.003, OR 2.2, 95% CI 1.3-3.8).

Following the exclusion of the anterosuperior margin of TSSJ, a significantly greater proportion of the projected A point was located within the TSSJ when compared with the projected B point (p < 0.001, OR 24.8, 95% CI 3.3-187.8). This result implied that using the B point as a bony landmark for the initial burr hole in temporal craniotomy carries less risk of major venous sinus injury.

Moreover, when the projected A and B point were not located at the anterosuperior margin or within the TSSJ, the projected B point had a greater accuracy in localization of initial burr hole and was also able to avoid inadvertent venous sinus injury. Almost all of the remaining projected B points were positioned above the anterosuperior margin of the TSSJ (48.3%) compared with the remaining projected A points which were mostly positioned around (above or below) the anterosuperior margin of the TSSJ (68.3%).

Our results suggest that when performing temporal craniotomy in Thais, the B point or the intersection between the squamosal suture and supramastoid crest, is a more reliable temporal bone landmark for localizing the anterosuperior margin of the TSSJ than the A point, which is the intersection between the squamosal and parietomastoid sutures. This is due to the B point consistent higher accuracy in correct identification, better predictable relationship, and lower risk of venous sinus injury.

In order to explain our results, we have to understand the controversy whether sutural landmarks such as the asterion are reliable or not.[14-16] In general, sutural landmarks can be used to "estimate" the location of major venous sinuses but with caution of individual variations.

One factor that makes sutural landmarks less accurate is the presence of additional, irregular sutural (Wormian) bones which make sutures more varied.[17] This presence of sutural bone is used to classify the asterion into type I (with sutural bone) and II.[18-19] However, the prevalence of type I asterion was round 10-20% and generally not mentioned in anatomical studies for surgical purposes.[1-7,9-10,15-16] Since the aim of our study was practical usage, we used only conspicuous suture lines. The prevalence of this bone is highest in the lambdoid suture followed by posteriorly located sutures such as parieto-mastoid suture.[20] This might explain our result that show how using 2 sutures is less reliable compared to the landmark which uses only 1 suture.

There are three factors that are known to affect skull size and shape and they may have impacted our results. The first factor is race, however, comparing races was not our goal. As our study population included only Thais, our results are very race-specific and might not be suitable for other ethnic groups.

The second factor is gender. However, Johnson et al. showed that the difference between races is larger than the difference between gender within the same race. Moreover, gender differences are also unique in each race.[21] We used equal proportions of both genders in our study to prevent selection bias. Our results showed that there were no statistically significant difference between gender regarding relationship between both skull landmarks and the anterosuperior margin of TSSJ.

Last but not least, the third factor is age. In early life, the human skull size and shape can change rapidly but there is minimal growth after 15 years.[22] In adults, bone resorption from increasing age can change cranial morphology.[23] However, this change might not be clinically significant. A study of cranial morphometry by Nikita showed that unlike gender, changes in cranial shape due to increasing age is not statistically significant and therefore it was justifiable to pool different age groups in a bioarcheological analyses.[24] Gapert and colleagues also studied the age effect on sexual dimorphism of adult

foramen magnum. They found no significant age effect, suggesting that a separation by age is not necessary.[25] From all this evidence, it is reasonable to generalize our results for Thai adults without age stratification.

CONCLUSION

The intersection between the squamosal suture and supramastoid crest serves as a more reliable temporal bone landmark for localizing the anterosuperior margin of TSSJ than the intersection between the squamosal and parietomastoid sutures. Most points with greater reliability were located at/or superior to the anterosuperior margin of the TSSJ.

We have no conflict of interest to disclose.

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Speech Outcome Analysis after Primary Cleft Palate Repair: Interim Siriraj Hospital Audit

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ABSTRACT

Objective: To evaluate the speech outcomes after primary cleft palate repair in a single tertiary medical institution of Thailand.

Materials and Methods: A prospective cohort study was performed. Patients who had cleft palate with/without cleft lip and underwent primary cleft palate repair were included. Speech assessment was performed using the Pittsburgh weighted speech score (PWSS) by a speech-language pathologist.

Results: Forty patients (21 males and 19 females) who underwent primary cleft palate repair at Siriraj Hospital were included. The median age at the time of speech evaluation was 7 years. The median age at primary cleft palate surgery was 12 months. The predominant cleft palate type was Veau 3 (47.5%). Oronasal fistula occurred 40%. Two-flap palatoplasty and intravelar veloplasty were the most common procedures. Median PWSS was 7, in which the competence velopharyngeal mechanism was found 5%, borderline competence 10%, borderline incompetence 32.5%, and incompetence velopharyngeal mechanism 52.5%. Among the velopharyngeal incompetence group, articulation disorder was the most common disorder with median score of 3. Besides, the median scores for nasality, nasal emission, phonation, and facial grimace disorder were 1, 2, 0 and 0, respectively. There was no statistically significant association between velopharyngeal incompetence and cleft types, age at primary surgery, type of operation, the width of cleft palate and prevalence of postoperative oronasal fistula or otitis media effusion.

Conclusion: Velopharyngeal incompetence has been commonly identified after cleft palate repair in our institute. The articulation disorder is the most common characteristic.

Keywords: Cleft palate; speech outcome; velopharyngeal insufficiency; craniofacial abnormalities (Siriraj Med J 2021; 73: 744-751)

INTRODUCTION

Cleft lip and/or cleft palate (CLP) are common craniofacial anomalies in Thailand. Chuangsuwanich et al., in 1998, reported that the incidence of patients with CLP was around 1 in 600 per live births at Siriraj Hospital.[1] Recently, Chowchuen et al. also reported a prevalence of CLP of 1.93 per 1000 live births in the northeast region of Thailand.[2] Patients with CLP have cosmetic and functional concerns, which typically require comprehensive multidisciplinary team (MDT) care and long-term follow-up, starting with cleft lip repair at around 3-6 months and cleft palate repair between 6-18 months of age.

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Cleft palate (CP) repair aims to create an anatomically intact and functional palate to improve feeding, achieve normal speech, and minimize maxillary growth restriction and middle ear infection.[3] In order to produce normal speech, a child must have velopharyngeal competence, defined as the ability to completely close the velopharyngeal sphincter, which separates the oro- and nasopharynx. The absence of this ability is termed velopharyngeal insufficiency.[4] The primary effects of velopharyngeal insufficiency are nasal air escape and hypernasality. A wide range of postoperative velopharyngeal insufficiency cases requiring secondary operation have been reported (15%–50%).[4-5]

The phonemic system in the Thai language is different from English. A Thai syllable consists of an initial, a vocalic nucleus, a final, and a tone.[6] The Thai language is a tonal language with sentences typically comprising a subject, verb, and object in order. The subject is usually not obviously stated but contextually assumed, similar to the case with the object. The verb has no declensions, tense, or conjugations.[7] According to this, if cleft palate patients have a decreased intelligibility of speech expression or are especially prone to articulation errors, it may disturb their communication skills, resulting in difficult social circumstances and communications.

Perceptual evaluation of speech by an experienced speech-language pathologist remains a widely accepted standard tool.[8-9] The Pittsburgh weighted speech score (PWSS), originally described by McWilliams and Phillips[10], is one of the key standardized methods used for a perceptual speech assessment. This tool rates the severity of velopharyngeal incompetency (VPI) by evaluating five speech components: nasality/resonance, nasal air emission, facial grimace, phonation/voice, and articulation.

Due to the lack of postoperative speech outcomes after CP repair in our centre, we conducted this study using PWSS to evaluate the postoperative speech outcomes after primary palatal repair.

MATERIALS AND METHODS

Patient enrollment

This research involved a prospective cohort study. Ethical approval was granted by the Institutional Review Board committee, Faculty of Medicine Siriraj Hospital, Mahidol University (Si 382/2018(EC2)). Informed consent was obtained. Patients who were diagnosed with CP with/without CL and underwent primary CP repair at Siriraj Hospital were enrolled. Exclusion criteria were syndromic patients with associated anomalies and patients who had follow-up time less than 3 years (co-operable assessment issue). After reviewing medical records, the eligible patients were contacted via telephone and invited for study participation.

Speech outcome assessment

The speech evaluation was conducted between October 2019 and 2020. Perceptual speech outcome assessments using PWSS were conducted face-to-face by a qualified speech-language pathologist (K.L.) (Fig 1). Five components were investigated: nasal air emission, facial grimace, nasality/resonance, phonation/voice, and articulation. The sum of scores equal to 0 indicated velopharyngeal competency, 1-2 indicated borderline velopharyngeal competency, 3-6 indicated borderline VPI, and ≥7 indicated VPI.

Data collection

The patients' medical records were reviewed to collect the following data: age and weight at primary palatoplasty, gender, cleft palate type based on Veau classification[11], cleft gap, techniques used in hard/soft palate procedures, the use of Vomerine flap, operation time, estimated blood loss, hospital length of stay, and the incidence of postoperative oronasal fistula (ONF) and otitis media effusion (OME). The Veau classification[11] categorizes cleft palate into four groups: Veau 1 (defects involving the soft palate only), Veau 2 (defects involving the hard and soft palate), Veau 3 (defects involving the soft palate to the alveolus, usually with lip involvement), and Veau 4 (complete bilateral cleft palate). Intraoral examination and photography were performed to identify postoperative ONF, defined as an abnormal connection or hole between the oral and nasal cavities, while intentionally unrepaired anterior hard palate and lingual–alveolar or labial–alveolar fistulas were not defined as this particular condition.

Statistical analysis

As appropriate, continuous variables were summarized using Mean ± standard deviation (SD) or Median (range). Categorical variables were summarized using counts with the percentage. The clinical and peri-operative characteristics between patients with and without VPI were compared using the Student's t-test or Mann-Whitney U test for continuous variables, while Pearson chi-square, Yates' continuity correction or Fisher's exact test was used for categorical variables, as appropriate. P-value of ≤0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.

Nasal Emission:

Not present _____0

Inconsistent, Visible _____1

Consistent, Visible _____2

Nasal escape on nasals appropriate _____0

Reduced _____0

Absent _____0

Audible _____3

Nasal Turbulence _____3

******Summary: Nasal emission scores: _____***

Phonation:

Normal ____0

Hoareseness or Breathiness

Mild ____1

Moderate ____2

Severe ____3

Reduced Loudness ____2

Tension in system ____3

Other_____

******Summary: Phonation scores:** ____*

Facial Grimace: ____2

Nasality:

Normal ____0

Mild Hypernasality ____1

Moderate Hypernasality ____2-3

Severe Hypernasality ____4

Hypo-Hypernasality ____2

Cul de sac resonance ____2

Hyponasality ____ 0

******Summary: Facial grimace and nasality scores:** ____*

Articulation:

Normal ____0

Development errors ____0

Errors from other causes not related to VPI ____0

Errors related to anterior dentition ____0

Reduced intraoral pressure for sibila nts ____1

Reduced intraoral pressure for other fricatives ____2

Reduced intraoral pressure for plosives ____3

Omission of fricatives or plosives ____2

Omission of fricatives or plosives plus hard glottal attacks for vowels ____3

Lingual-palatal sibilants ____2

Pharyngeal fricatives, snorts,inhalation or exhalation substitutions ____3

Glottal stops ____3

Nasal substitutions for pressure sounds ____4

******Summary: Articulation scores:** ____*

******TOTAL SCORE (from all sections above): ____

Speech Indicates:

____0 Competent Velopharyngeal Mechanism

____1-2 Competent to Borderline Competent

____3-6 Borderline to Boderline Incompetent

____7 Incompetent Velopharyngeal Mechanism

Fig 1. Perceptual speech evaluation form adapted from the Weighted Values for Speech Symptoms Associated with Velopharyngeal Incompetence of the Cleft Palate Center of the University of Pittsburgh[10]

RESULTS

Forty patients (21 males and 19 females) with CP between 3-15 years of age who underwent primary cleft palate repair in Siriraj Hospital were included in the study. The median age at primary palatoplasty was 12 months old (range 8-40). Veau type 3 was found in 47.5% of patients, while Veau type 4, type 2, and type 1 were found in 30%, 15%, and 7.5%, respectively. The mean cleft gap width was 12.3 mm. The Bardach two-flap palatoplasty technique was performed in 94.6% of patients, while 5.4% underwent Veau-Wardill-Kilner palatoplasty for hard palate surgery. Intravelar veloplasty was performed in 82.5% of patients, while 2.5% underwent radical intravelar veloplasty, and 12.5% underwent Furlow z-plasty for soft palate surgery. One patient (2.5%) has unknown detail of the soft palate procedure. The vomerine flap was used in 42.5% of patients. The mean operation time was 127 min. Table 1 summarizes the patients' demographic data.

At the time of speech evaluation, the median age was 7 years (range 3-15 years). Among 40 patients, 21 (52.5%) had VPI, while 13 (32.5%) had borderline VPI, and 4 (10%) had borderline velopharyngeal competency, and 2 (5%) had velopharyngeal competency. The median total PWSS score was 7.0 (0-18). Median score for nasal emission was 2 (0-3), phonation was 0 (0-5), facial grimace was 0 (0-2), nasality was 1 (0-4), and articulation was 3 (0-10) (Table 2). There was no significant difference in age at primary palatoplasty, or for the type and width of cleft palate, type of surgery for hard and soft palate, or incidence of postoperative ONF and OME between patients with or without VPI (data shown in Table 3).

Overall, 16 patients (40%) had postoperative ONF. All of those underwent fistula closure operations. However, 8 patients had recurrence fistula at the time of speech evaluation. The median interval between primary CP surgery and ONF occurrence was 22 months (range 3-40 months). OME was found in 30 patients (75%).

DISCUSSION

We present interim data on the perceptual speech outcomes after primary cleft palate repair from a tertiary referral centre in Thailand. We found over half of our patients with CP had postoperative VPI after primary CP repair at around 7 years of age. Moreover, making articulation errors was the most common characteristic affecting achieving a higher PWSS.

Normal speech achievement is one of the most important goals of CP surgery. Perceptual evaluation (i.e., listening) is the "gold standard" clinical assessment method for speech and voice disorders in the cleft palate population, and has been used in several previous studies.[8,12-16] In this study, VPI was identified by perceptual speech evaluation using PWSS in 53% of patients. This rate is higher than those reported in prior studies, ranging from 15% to 45%.[4-5] Articulation errors were found to be the most common speech distortions in our series. Pratanee et al., in 2016, found that articulation errors were the most common speech and language defects in Thai cleft palate patients.[17] Oopanasak et al. organized a case-control study of Thai children aged 6-13 years old and found that patients with CLP had significantly higher articulation defects than normal children, with velar and trill errors the most common articulation patterns.[18] Another study in Saudi Arabic-speaking children aged between 6-15 years old by Albustanji et al. found speech abnormalities, including articulation, hypernasality, and resonance, in 74% of patients after CP repair.[19] A study from Korea reported that 20% of patients had postoperative VPI and 50% demonstrated articulation deficits.[20] Recently, a study of Arabic-speaking Egyptian children between 3-9 years old demonstrated that articulation disorders, especially substitution, were the most common errors in CP patients with VPI.[21]

There are many factors involved in articulation. Every element of the speech apparatus, including the lips, teeth, palate, tongue, velum, and larynx, are engaged in producing intelligible sounds.[22] Patients in our study were evaluated at 7 years old, which is in the mixed dentition phase. Abnormal dental alignment (e.g., severe crowding), including transverse maxillary collapse during this time, maybe a causative factor in articulatory disorders in cleft palate patients. Another factor, including the prevalence of remaining alveolar cleft during this particular phase, may interfere with the incidence of articulation errors. Significantly, most children with CP in our study did not receive any regular long-term speech therapy after surgery. Although speech therapy in Thailand is offered to cleft palate patients free of charge due to our universal health care program, regular long-term speech therapy can be burdensome. Ideally, patients are required to attend 30-minute speech therapy sessions at least every 2-3 months for several years. Further, the speech therapy service is only available in a restricted number of tertiary referral hospitals. In addition, as the patients are children, their parents need to accompany them to the hospital for the service. This would cost them transportation expenses and a need to miss work, resulting in reduced income. Therefore, access to and take-up speech therapy in our patients is limited, especially when considering the long distance to the service and socioeconomic status of many of our patients' families.[23-24] Unsurprisingly, many

TABLE 1. Demographic data of 40 patients with cleft palate who underwent primary cleft palate repair.

Characteristics	(Total=40)
Genders, number (%)	
Male	21 (52.5%)
Female	19 (47.5%)
Surgeons	
Attending staff	33 (82.5%)
Trainees	7 (17.5%)
Age at primary palatoplasty (months), Median (range)	12 (8-40)
Age at speech assessment (years), Median (range)	7 (3-15)
Cleft types, number (%)	
Veau type I	3 (7.5%)
Veau type II	6 (15%)
Veau type III	19 (47.5%)
Veau type IV	12 (30%)
Cleft gap width (mm.), Mean ± SD	12.3 ± 4.1
Type of hard palate procedure, number (%)	Total 37
Two-flap palatoplasty	35 (94.6%)
Veau–Wardill–Kilner palatoplasty	2 (5.4%)
Type of soft palate procedure, number (%)	Total 40
Intravelar veloplasty	33 (82.5%)
Radical intravelar veloplasty	1 (2.5%)
Furlow Z-plasty	5 (12.5%)
Unknown detail of the procedure	1 (2.5%)
Vomerine flap use, number (%)	17 (42.5%)
Blood loss (ml.), Median (range)	20 (1-150)
Surgery duration (minute), Mean ± SD	127 ± 49
Hospital stay (days), Mean ± SD	4 ± 1
Presence of oronasal fistula, number (%)	16 (40%)
Presence of otitis media effusion, number (%)	30 (75%)
Speech indicates, number (%)	
Velopharyngeal competency	2 (5%)
Borderline velopharyngeal competency	4 (10%)
Borderline VPI	13 (32.5%)
VPI	21 (52.5%)

TABLE 2. Modified weighted values for speech symptoms associated with velopharyngeal incompetence of the Cleft Palate Center of the University of Pittsburgh by perceptual evaluation.

Modality	Score
Total : Median (range)	7 (0-18)
Articulation : Median (range)	3 (0-10)
Nasality : Median (range)	1 (0-4)
Nasal emission : Median (range)	2 (0-3)
Phonation : Median (range)	0 (0-5)
Facial grimace : Median (range)	0 (0-2)

TABLE 3. Various parameters and the association with VPI.

Parameter	PWSS < 7 (n= 19)	PWSS ≥ 7 (n= 21)	P-value
Age at primary palatoplasty, Median (range) (months)	12 (8-40)	12 (9-39)	0.539
Cleft types, number (%)			
Veau type I	3 (15.8)	0 (0)	0.238
Veau type II	3 (15.8)	3 (14.3)	
Veau type III	7 (36.8)	12 (57.1)	
Veau type IV	6 (31.6)	6 (28.6)	
Cleft gap width, Mean ± SD (mm.)	12.2 ± 3.4	12.3 ± 4.7	0.909
Type of hard palate procedure, number (%)			
Two-flap palatoplasty	16 (84.2)	19 (90.5)	0.495
Veau–Wardill–Kilner palatoplasty	0 (0)	2 (9.5)	
Type of soft palate procedure, number (%)			
Intravelar veloplasty	13 (68.4)	20 (95.2)	0.130
Radical intravelar veloplasty	1 (5.3)	0 (0)	
Furlow Z-plasty	4 (21.1)	1 (4.8)	
Vomerine flap use, number (%)	7 (36.8)	10 (47.6)	0.713
Presence of oronasal fistula, number (%)	6 (31.6)	10 (47.6)	0.477
Presence of otitis media effusion, number (%)	15 (78.9)	15 (71.4)	1.000

factors, not only velopharyngeal anatomical deficiencies, are associated with VPI in our patients in this centre.

Our study revealed no significant association between age at primary surgery, types and width of cleft palate, type of CP surgery, or incidence of postoperative ONF, OME, and severity of VPI. These data are consistent with a previous study from a tertiary university hospital in Northeast Thailand.[25]

Postoperative ONFs in cleft palate have been reported in 9%-50% of cases.[26-27] The ONF rate in the present study was 40%, which is consistent with previous literature.[28-31] A large case series from Khon Kaen University, Thailand, revealed that ONF formation was significantly associated with higher types of Veau classification, syndromic cleft patients, and a cleft width more than 11.5 mm.[32] In our series, we found that the majority of patients had Veau type 3 or 4 (77%), and the mean cleft gap was 12.3 mm. From our study, 48% of patients with VPI had postoperative ONF. Although an ONF closure procedure was performed in all these patients, 50% still had residual fistula at the time of the study. In the borderline VPI group, 38% of patients had ONF. Also, 60% of those still had residual ONF at the time of the study despite a fistula closure procedure having been performed. There were no ONF cases in the velopharyngeal competency and borderline velopharyngeal competency group. ONF might be the cause for this, producing a higher hypernasality score in the PWSS.

OME is common in CLP, often resulting in hearing loss, speech delay, and learning disabilities. If untreated, chronic otitis media or cholesteatoma may occur, leading to permanent middle ear damage. In our hospital, the prevalence of OME was reported by Ungkanont et al. to be around 50%–80%.[33] They also found a significant improvement in the audiograms after palatoplasty. In this series, we found 75% of patients had OME. This condition might be another confounding factor that affected the poor speech outcomes in this study, despite the statistical analysis suggesting no significant association between OME and speech outcomes in this study. Further subgroup analysis should be performed to confirm this outcome.

We realize that one of the significant limitations of our study was the small population sample. We had previously planned to enrol a study population of 200 by calculating the predicted sample size using nQuery Advisor (San Diego, CA) and by assuming the rate of velopharyngeal incompetency as 37.5% with confidence interval of 95%. However, due to the COVID-19 pandemic in Thailand during 2020, we, unfortunately, could only enrol 40 patients to take part in face-to-face speech evaluation. Ongoing speech evaluations are continuing for a complete long-term speech outcome assessment.

This interim study should, however, be of benefit for our hospital and can reinforce the need for MDT care, including cleft surgeon, speech pathologist, ear nose throat surgeon, and dental team, which is mandatory for all patients with CLP. Objective investigations, such as nasendoscopy and/or video-fluoroscopy, should be further used in patients who have VPI from initial perceptual speech evaluation as the diagnostic tools and preoperative planning before any subsequent correction procedure.

CONCLUSION

Postoperative VPI is common after cleft palate repair in our hospital. The articulation disorder is the most common characteristic affecting speech outcomes. We encourage establishing a cleft and craniofacial centre to deliver MDT care in our hospital to achieve the best benefits in CLP care.

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Clinical Efficacy Test of Polyester Dressing Containing Herbal Extracts and Silver Sulfadiazine Cream Compared with Silver Sulfadiazine Cream in Healing Burn Wounds: A Prospective Randomized Controlled Trial

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ABSTRACT

Objective: The most common method of burn wound care is the application of silver sulfadiazine cream with sterilized gauze covering. However, conventional gauze fabric with a large pore size may stick to the wound bed and cause wound trauma, leading to the delay of healing and pain. The non-adherent property of a hydrocolloid dressing coated with herbal extract (SI-HERB) can promote wound healing as well as reduce pain. Thus, this study aims to compare clinical efficacy between a "polyester dressing containing herbal extracts and silver sulfadiazine cream" and "silver sulfadiazine cream" alone in second degree burn wound healing.

Materials and Methods: This study compared the two methods of burn wound treatment in the same patients, who were randomly split into a "treatment group", which were applied both silver sulfadiazine cream and hydrocolloid dressing, and "control group", which were applied only silver sulfadiazine cream. The studied outcomes were the number of days for wound closure, the percentage epithelialization, and the pain score. In total, 24 patients at the Burn Unit, Siriraj Hospital were enrolled in this study.

Results: The wound areas were initially ranged from 210–220 cm^2. The treatment group exhibited significant results regarding faster wound healing, referring to the number of days of wound closure (18 days in the control group vs. 15 days in the experimental group) and the percentage epithelialization compared to the control group. The average pain score in the experimental group was also lower on days 9, 12, and 15 after treatment ($p < 0.05$). No adverse effects were observed during the study.

Conclusion: The combination of hydrocolloid dressing and silver sulfadiazine cream could reduce the wound shearing force and wound bed injury, accelerating the rate of wound closure and decreasing the pain during changing the dressing. This technique could improve upon the standard burn wound treatment.

Keywords: Burn; wound; silver sulfadiazine cream; hydrocolloids dressing (Siriraj Med J 2021; 73: 752-757)

INTRODUCTION

Wounds involve a breakdown of the protective function of the skin and the loss of continuity of the epithelium, with or without the loss of underlying connective tissue (i.e., muscle, bone, nerves). Although the body system itself has the ability to heal, there are many factors

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that can affect wound healing, such as age, nutritional status, immunization status, co-morbidity, and the types of wound. Wound care aims to accelerate the healing process and prevent complications that could prolong the wound healing process and length of hospital stay. Wide, open wounds, especially burn wounds, can easily become infected and require a prolonged hospital stay. This can cause an increase in the cost of burn wound care by up to 15,000 USD on average per person.[1] Previous studies have reported a correlation between the area and depth of the burn wound and the cost of treatment.[2,3] Therefore, shortening the healing process may lead to less complications, a decrease length of hospital stay and hospital costs, and also better quality of life of the patients.[4]

Burn wounds are categorized into 3 degrees of burn according to the depth. A first degree burn can heal itself without intervention in a week. A second degree burn can heal with an epithelialization process; however, it can turn to a third degree burn if not properly managed.[5] A third degree burn needs surgical intervention for promoting the healing process. This study focuses on second degree burn wounds.

The most common method of burn wound care in Asia is the application of silver sulfadiazine cream (SSD) with sterilized gauze covering. SSD is composed of silver nitrate, which provides a bactericidal effect, and sodium sulfadiazine for its bacteriostatic property. SSD has a broad spectrum antimicrobial action with wound healing nurture.[6] However in clinical application, there are various factors that are hard to control, such as the thickness of the cream and the amount of cream per area, which are varying in practitioner. Also, the gauze absorbs the SSD, it can dry up and adhere to the wound bed. While peeling the gauze out to change the dressing, this can create a shearing force on the wound bed, causing wound bed trauma and thus slowing the wound healing process.

Lipido-colloid dressing was developed to increase the interval of wound dressing, reduce pain during dressing, due to the decrease adherence between the wound and the gauze dressing.[7] However, the major problem for this treatment is the cost since these products have to be imported.

Our previous study investigated a product comprising a hydrocolloid dressing coated with herbal extract, called SI-HERB.[12] This product has absorption capacities, drainage abilities, and it does not stick to the wound. Furthermore, it is locally made in Thailand and only costs one dollar per piece. It has no clinical side effects and it has already been approved by the Thai FDA. The herbal extracts in this material comprise *Centella asiatica* and Aloe Vera, which show anti-microbial effects, accelerate wound healing, moisten the wound, and show anti-inflammatory effects.[8,9] Some studies have indicated that these two substances can heal a wound faster than SSD.[10,11] Research from Muangman et al. in 2016 compared SI-HERB with old fashioned polyester (Bactigras), and showed that SI-HERB was superior in wound healing and improving tissue regeneration, with a lower cost of treatment and less pain during wound care.[12]

Consequently, this study used a hydrocolloid dressing coated with herbal extract (SI-HERB) combined with SSD on a dermal burn wound, which had some part of the eschar remaining on the wound surface, compared with using SSD alone. We hypothesized that the results would show better wound healing than using SSD alone.

Objective

The objective of this study was to compare the clinical efficacy between a "polyester dressing containing herbal extracts and silver sulfadiazine cream" and "silver sulfadiazine cream" alone in second degree burn wound healing regarding the number of days for wound closure, the percentage epithelialization, and the pain score of patients.

MATERIALS AND METHODS

Population

In total, 24 patients were included in this study. The patients, aged between 18 to 60 years old, had at least two second degree burn wounds. Each patient's burn wound was at least 150 cm^2 in area (approximating to 10% of body surface area by Wallace's rule of nine). The patients were ASA class I or II and ECOG 0 before getting burn wounds. Patients with history of allergy to silver, sulfadiazine or herbal products were excluded. Pregnant, breastfeeding, diabetes, or immunocompromised patients were also excluded from the study.

Study design

This was a single-center, prospective, randomized controlled study comparing wound dressing with a polyester dressing containing herbal extracts and silver sulfadiazine cream with silver sulfadiazine cream alone in second degree burn wound healing. This study was conducted at the Burns Unit, Division of Trauma Surgery Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok. The data were obtained between January 2019 and June 2020.

The second degree burn wounds of at least 150 cm^2 with some areas of eschar in the recruited patients were

randomly allocated to one of two treatment groups. In each patient, after an accurate debridement and cleaning of the burn wound with appropriate steriled normal saline solution, each burn wound size was evaluated by a registered nurse uninvolved with the dressing wound team. Photos of the burn wound were taken and evaluated in terms of size using the Image J program. Burn wound dressing was performed according to the treatment group. In the experimental group, patients were covered with SSD and a polyester dressing containing the herbal extracts. In the control group, they were covered with SSD. All the burn wounds were covered with steriled gauze, gamgee, and tape.

Evaluation was done every 3 days. Photos of each burn wound were taken and the size evaluated using the Image J program. Pain was evaluated by using the visual analog scale (VAS) range 0-10. Complications and other intervention needs were assessed by medical doctors. The evaluation and assessment team were not involved in the dressing procedure.

Wound healing was measured as the %epithelialization calculated by the formula below.

$$\%\text{Epithelialization} = \frac{(\text{Area of initial wound} - \text{Area of wound at exam date})}{\text{Area of initial wound}} \times 100$$

Ethics and material safety

Written informed consent was obtained from each patient or relatives prior to their participation in this study. The study was conducted in accordance with the international code of medical ethics. Patients could withdraw their consent whenever they felt uncomfortable and wished to finish the trial. The trial protocol and subsequent amendments including ethical approval were reviewed and approved by the Human Research Protection Unit, Siriraj Institutional Review Board (SIRB), Thailand.

This product, the polyester dressing containing herbal extracts, is already approved by the Thai FDA. There was no clinical side effects in the previous study utilizing this product.[12]

Statistical analysis

Demographic data are described with descriptive statistics. Quantitative data are described in terms of the mean ± standard deviation, or median (P25, P75). Quantitative data are described in frequency (percentage)

The differences between the treatment groups were evaluated using the paired t-test or Wilcoxon signed ranks test. The difference at each point in time was analyzed by repeated-measure ANOVA. For the qualitative variables, we used Pearson's Chi-square test or Fisher's exact test. All the statistical tests for efficacy were two-sided, with an alpha level = 0.05.

RESULTS

There were 24 second degree burn wound patients eligible for this study. Most were male patients (62.5%). The average age of the patients was 40.13 ± 14.20 years old. The total burn surface area was 35.35% in average. The average hospital stay was 41.96 ± 22.39 days. The most common cause of the burn wounds was scald burns in 35.35 ± 17.49% of cases, as shown in Table 1.

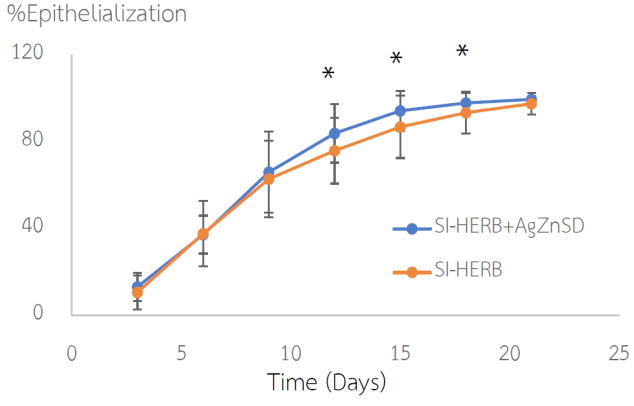
TABLE 1. Demographic data of the burn wound patients included in the study.

Demographic data	
Male patients	15 (62.50%)
Age (year)	40.13 ± 14.20
Burn percentage (%)	35.35 ± 17.49
Hospital stay (day)	41.96 ± 22.39
Causes	
Flame burn	9 (37.50%)
Scald burn	14 (58.33%)
Electrical burn	1 (4.17%)
Underlying diseases	
Hypertension	4 (16.67)
Hypercholesterolemia	1 (4.17)

The burn wounds of each patient were randomly assigned in both treatment groups. The experimental group was applied polyester dressing containing the herbal extracts and silver sulfadiazine cream. The control group was applied silver sulfadiazine cream alone. The initial burn wound area was not statistically significantly different between the two treatment groups: 219.15 ± 52.09 and 211.04 ± 46.18 cm^2 in the experimental and control group, respectively.

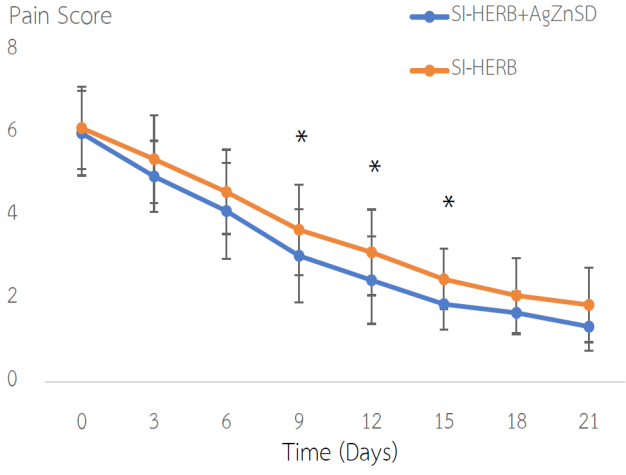
The percentage epithelialization calculated using the formula above is shown in Graph 1. The percentage epithelialization was similar in both groups at day 3 after treatment, at 10%. After that, the percentage epithelialization

rose, especially in the experimental group, as shown in Graph 1. The differences in the percentage epithelialization were statistically different at days 12, 15, and 18 ($p<0.05$). The wounds were more than 90% healed after 12 days and 15 days in the experimental group and control group, respectively. The wounds in the experimental group were completely healed in 15.04 ± 3.76 days on average. This was significantly faster than in the control group, which took 18.04 ± 3.74 days to heal on average ($p < 0.05$).



Graph 1. Percentage epithelialization and days for treatment comparing the experimental group and the control group.

The pain scores were rated by each patient every three days of the experiment and the scores are shown in Graph 2. The initial pain scores were not different in the experimental group and the control group (6.0 ± 1.0 and 6.1 ± 1.0, sequentially). The pain score decreased as time goes on. The experimental group had significantly lower pain scores on days 9, 12, and 15 ($p<0.05$).



Graph 2. Pain scores every three days of treatment comparing the experimental group and the control group.

Some examples of burn wound patients and the wound healing progression are shown in Figs 1-6. These pictures show the progression of the burn wound from initial of treatment until completely heal.

Fig 1. Example photos of the first patient in the control group

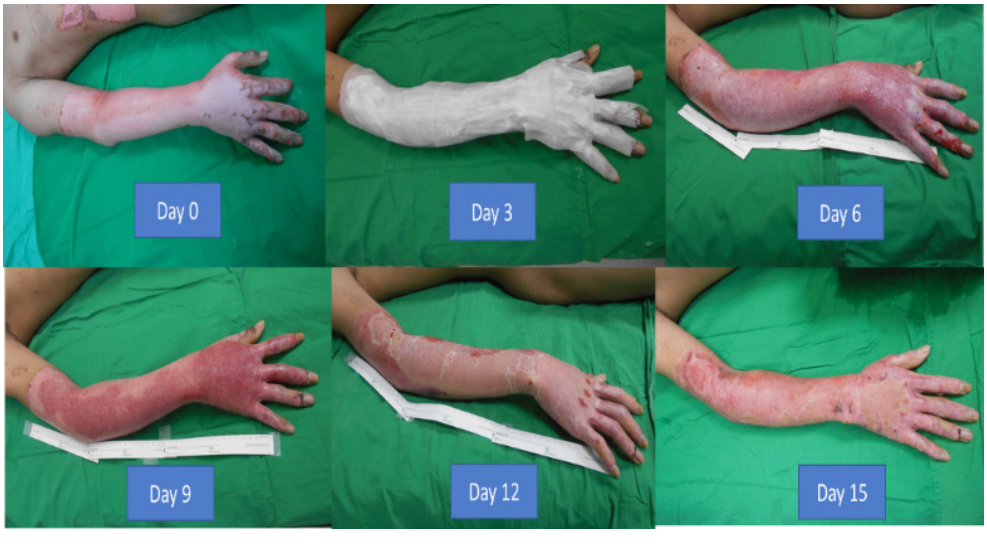


Fig 2. Example photos of the first patient in the experimental group

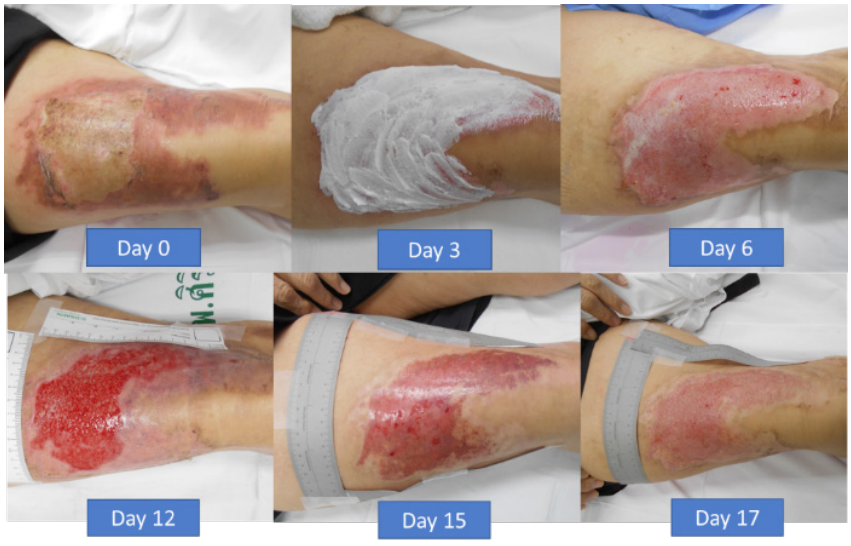


Fig 3. Example photos of the second patient in the control group

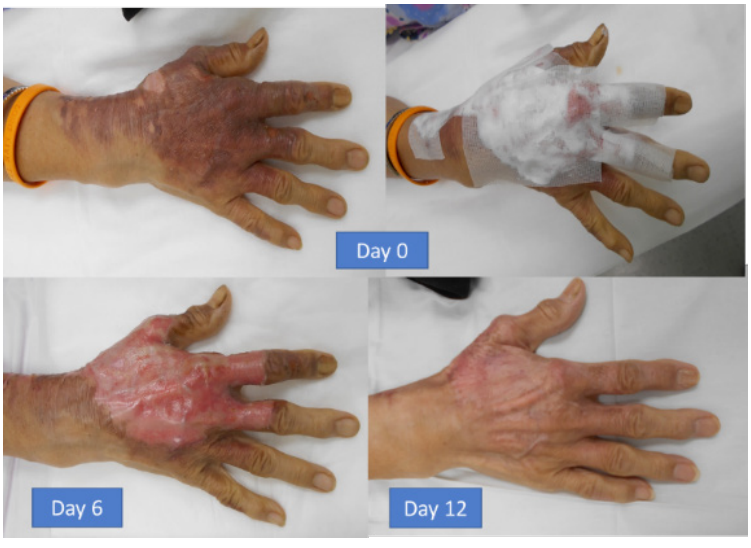


Fig 4. Example photos of the second patient in the experimental group

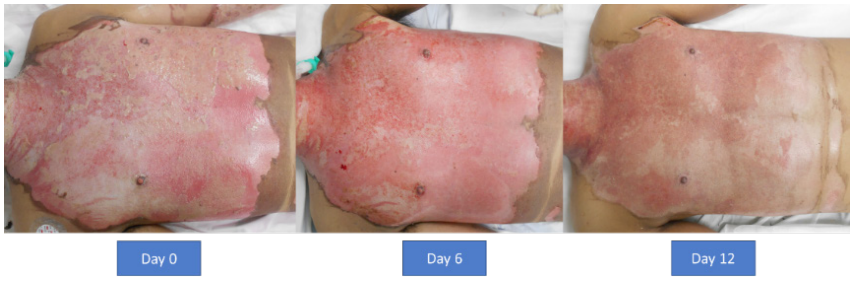


Fig 5. Example photos of the third patient in the control group

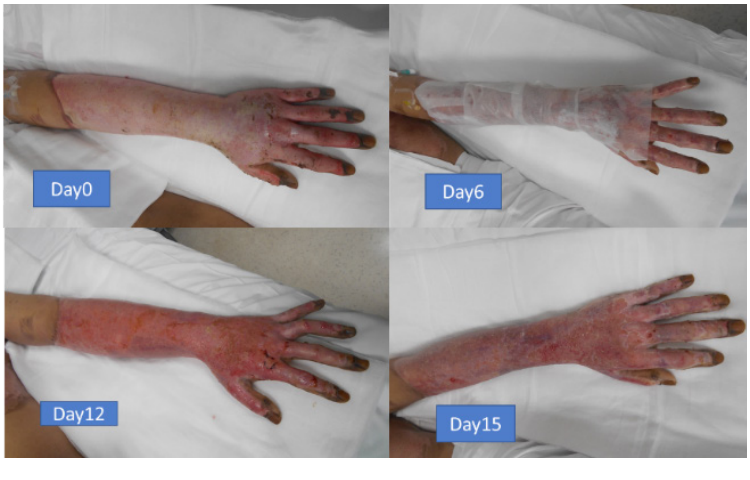


Fig 6. Example photos of the third patient in the experimental group

DISCUSSION

This study showed that wound dressing with polyester dressing containing herbal extracts and SSD had a better outcome compared to SSD alone in terms of the days taken for wound closure, the percentage epithelialization, and the pain scores of the patients. This was due to the non-adhesive properties of the dressing to the wound, causing less trauma to the newly generated epithelium.

This study showed similar results for the days taken for wound closure as our previous study in 2016, which reported an average of 15 days for wound closure, which was 2 days faster than the group with the wound not covered with the polyester dressing containing herbal extracts.[12]

The herbal extracts in this product, namely *Centella asiatica* and Aloe vera, had antimicrobial properties. Such an antimicrobial property has previously been reported in an Aloe vera-containing dressing (Barkat et al., 2017 and Khorasani et al., 2009) and *Centella asiatica*-containing dressing, with both showing significant efficacy.

The limitation of this study to note is that the study was not double-blinded. Patients inevitably knew the treatment of each burn wound. Another limitation is the pain scores that were rated by the patients. Sometimes it can be difficult to distinguish pain from each burn wound part in the body.

CONCLUSION

This study can conclude that for second degree burn wounds with some degree of eschar on top of the wounds, the use of a polyester dressing containing herbal extracts combined with silver sulfadiazine cream can promote better wound healing and cause less pain without any clinical side effects.

This treatment strategy might be included in the standard burn wound care protocol in the future to improve burn wound care. Further cost-analysis research might be helpful in future implementation of this treatment in the protocol.

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Intraoperative Problems and Solutions in Pneumovesicum Laparoscopic Cross-trigonal Ureteral Reimplantation in Children by a Beginner Surgeon

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ABSTRACT

Objective: Many beginner surgeons feel anxious when first doing the procedure. Some may encounter many intraoperative difficulties or problems, resulting in abandoning the technique. We will demonstrate our methods and the solutions to major intraoperative problems.

Materials and Methods: A beginner surgeon performed the operation on 13 children with VUR (20 ureters) who met the indications for surgery between October 2016 and August 2017. Age ranged from 2 to 7 years. Each operation comprised 2 main steps: anchoring the urinary bladder wall to the anterior abdominal wall under cystoscopic vision, followed by a cross-trigonal ureteral reimplantation under pneumovesicum laparoscopy. The intraoperative problems, postoperative care, and follow-up periods were recorded to identify surgical outcomes.

Results: Most significant, intraoperative problems were air leakage, bleeding, tear of the bladder mucosa above the tunnel, and inability to insert a tube into the ureter pre- and post-reimplantation. Most problems could be managed. Only one case had to be converted to open reimplantation due to uncontrolled air leakage. Postoperatively, 2 patients had hydroureteronephrosis at 4 weeks, but it eventually spontaneously regressed. One patient had cystitis, treated with oral antibiotics. Between the 1-year and 4-year follow-up, no patients had hydroureteronephrosis or urinary tract infections (UTI).

Conclusion: Pneumovesicum laparoscopic ureteral reimplantation is a feasible technique for beginner surgeons. Although many intraoperative problems may be encountered, most can be managed, resulting in the completion of the laparoscopic procedure.

Keywords: Vesicoureteral reflux; pneumovesicum laparoscopic ureteral reimplantation; vesicoscopic ureteral reimplantation; beginner surgeon (Siriraj Med J 2021; 73: 758-762)

INTRODUCTION

Although many of the patients diagnosed with vesicoureteral reflux (VUR) may recover spontaneously with conservative treatment, a large number meet the indications for anti-reflux interventions. Injection therapy is now more popular because of its endoscopic approach that can be done in an outpatient setting and is more cost-effective than open ureteral reimplantation, especially for low-grade VURs.[1,2] In contrast, for high-grade VURs, ureteral reimplantation is considered a suitable option due to the lower success rate of injection therapy.[3] In many countries, including Thailand, no injection materials are

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used due to high cost. Consequently, ureteral reimplantation remains the option of choice for VUR treatment.

Like many other operations, ureteral reimplantation can be performed using open and/or laparoscopic methods. Based on our experience, laparoscopic surgery, in general, is associated with less pain, shorter lengths of hospital stay, rapid recovery, and better cosmesis than open approach. The same applies to the ureteral reimplantation procedure. Laparoscopic ureteral reimplantation employs 2 techniques: an extravesical and an intravesical approach. Because of concerns about postoperative voiding dysfunction, extravesical ureteral reimplantation is considered inferior to the intravesical technique, especially for bilateral reimplantation. A novel technique, transvesicoscopic Cohen ureteral reimplantation under carbon dioxide bladder insufflation, was first reported by Yeung et al. in 2005.[4] They demonstrated a high success rate for this method (96%), which is comparable with the conventional open intravesical Cohen cross-trigonal technique. This technique is currently in widespread use and is still employed to treat VUR.

For young pediatric urologists, laparoscopic procedures in children are hard to perform and require more learning than those for adults. This is not only because of the very small working space available in a little body, but also due to relatively few cases. Many beginner surgeons therefore face a steep learning curve. Compared to a pneumoperitoneum, a pneumovesicum has much less working space, resulting in more difficulty in performing a vesicoscopic ureteral reimplantation. This paper describes the experience gained in performing this operation by a beginner surgeon, the intraoperative problems encountered, and the solutions developed. The content should enable other beginner surgeons to undertake this operation with a degree of confidence and encourage them to perform further laparoscopic surgeries in children.

MATERIALS AND METHODS

Patients

From October 2016 to August 2017, a urologist, who recently finished his residency training in June 2016, carried out pneumovesicum laparoscopic ureteral reimplantation in 20 ureters of 13 patients with VUR. Their ages ranged from 2 to 7 years at the time of surgery. They all were followed until mid-2021.

Surgical technique

Cystoscopy. After general anesthesia was administered, each patient was placed in the lithotomy position. The abdomen and external genitalia were prepared and draped in a sterile fashion. Transurethral cystoscopy with a 30-degree lens and normal saline irrigation was performed. The bladder was carefully inspected, and both sides of the ureteral orifices were identified before the bladder capacity was measured. Normal saline was filled in the bladder again until maximum anesthetic capacity was reached.

Bladder wall anchoring and ports placement. The next step was to anchor the bladder wall to the anterior abdominal wall. This procedure prevented bladder collapse during the operation. Under cystoscopic vision, two, 24-gauge, Medi-Cut needles were passed into the bladder at the midline of the suprapubic site, which corresponded to the most anterior part of the bladder wall that had been observed from the cystoscopy. In this step, there is a need to be aware of the peritoneal recess, which may go down to cover the superior part of the anterior bladder wall. Number 1 nylon was first inserted into one Medi-Cut needle. Grasping forceps for cystoscopy were subsequently inserted into the other needle in order to grasp the end of the nylon, pull it up, and tie both ends of the nylon together, thereby anchoring the bladder wall. Using the same technique, two other anchoring stitches were sequentially placed on the Langer's at Langer line, just lateral to the site where the working ports would be placed. A 5-mm camera port was placed below the midline anchoring stitch using an open technique. Another two, 5-mm working ports were placed under laparoscopic vision on the Langer line (Fig 1). Placing the working ports on the Langer's line facilitated the later dissection of the ureter and creation of the submucosal tunnel. The bladder was then drained and insufflated with carbon dioxide at a pressure of 10–12 mmHg via a camera port at the bladder dome.

Ureteral dissection and tunnel creation. A size 5 to 6 Fr feeding tube was inserted into the ureteral orifice. This tube facilitated the visualization of the ureter's contour and its serosa. The medial side of the ureteral orifice was hung with 4–0 chromic catgut or Vicryl. Dissection of the ureter was performed with the hook. Blood vessels on the serosa of the ureter were clearly visualized under the laparoscope. When the ureter was freely dissected, a cross-trigonal submucosal tunnel was created with sharp scissors. The ureter was mobilized through the tunnel and fixed into position with 4–0 Vicryl. The gap of the muscular layer at the ureteral hiatus was sutured to prevent the future formation of a diverticulum. The ureter serosa was fixed to the hiatus before the bladder mucosa was closed. The feeding tube was placed in the

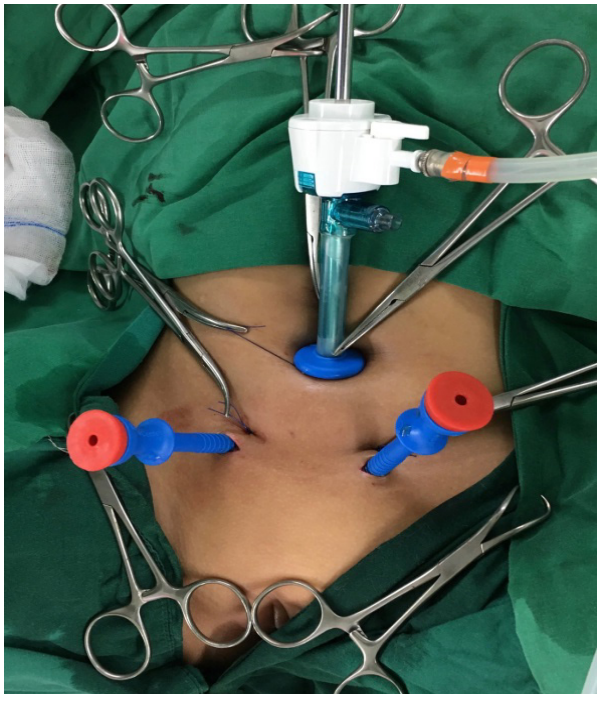

Fig 1. Position of all ports

ureter to enable splinting via the working port. The working port was removed, but the feeding tube was left and fixed to the skin with Number 3 nylon. A Foley catheter was placed. The camera port was removed, and cystoplasty was performed using an absorbable suture. The anchoring stitches were removed, and the abdominal sheath and skin were closed.

Postoperative care and follow-up. General routine postoperative care was conducted. A ureteral stent was used for about 6 to 7 days, and the Foley catheter was removed 1 day after the ureteral stent removal. Without any catheter, the patient could then be discharged from the hospital. The patient was scheduled for a urinalysis and kidney-bladder sonography at 4 weeks postoperatively. If no abnormal symptoms or findings were found at that time, the patient was rescheduled to see us every 3 months postoperatively in the first year and every year with ultrasound afterwards. Voiding cystourethrography would be repeated in case of persistent hydronephrosis or febrile UTI. Prophylactic antibiotics was discontinued at 6 months after surgery if the patient had improved hydronephrosis and no febrile UTI.

RESULTS

The mean age of the patients was 4 years 6 months (range: 1 year 10 months to 6 years 5 months). Six patients had unilateral VUR, while seven had bilateral VUR; a total of 20 ureters were reimplanted without tapering of the ureters. The mean bladder anesthetic capacity was 302 mL (range: 200 to 450 mL). The mean operative time (from cystoscopy to wound closure) was 176 minutes (range: 140 to 205 minutes) for the unilateral reimplantations and 240 minutes (range: 180 to 371 minutes) for the bilateral reimplantations. Table 1 details the demographic data and operative times of all 13 cases. In our experience, the intraoperative problems were air leakage (4 cases), bleeding (3 cases), tear of the bladder mucosa over the tunnel (2 cases), and inability to insert the ureteral stent (1 case). The whole operation managed to be performed for almost all of the patients. The procedure for only one patient (who was the youngest, aged 1 year and 10 months) had to be converted to an open reimplantation because of uncontrolled air leakage into the extravesical space and severe bladder collapse.

No patient had significant postoperative complications. They occasionally had gross hematuria for only a few days. They could start ambulating on postoperative day 1. Bladder spasm was minimal with no anti-muscarinic administration. The ureteral stent was left in the reimplanted ureter for 7 days. The urethral catheter was removed one day after the ureteral catheter removal, following which the patients were discharged home. A follow-up was conducted 4 weeks later. A urinalysis and kidney ultrasonography were carried out on all patients. If both tests were normal and the patients had no abnormal symptoms, they were scheduled for a further follow-up 3 months postoperatively. One patient was found to have dysuria, frequent urination, and pyuria at the initial two follow-ups. She received oral antibiotics and recovered fully during the following 2 weeks. Two patients with grade 5 VUR were found to have hydronephrosis in the first follow-up. However, the degree of hydronephrosis had improved by the next 4-week follow-up. Between the 1-year and 4-year follow-up visits, none of the 13 patients exhibited a dilated ureter or hydronephrosis in an ultrasound examination, and there were no signs or symptoms of urinary tract infections.

DISCUSSION

A minimally invasive technique for intravesical cross-trigonal ureteral reimplantation was reported by Gill et al. in 2001.[5] They used a transurethral endoscope, and 2 working balloon-ports were placed at the suprapubic area. However, this technique had some limitations, such as not being suitable for bilateral reimplantations and problems with the original ureteral hiatus. In 2005, Yeung et al. reported the first series of transvesicoscopic Cohen ureteral reimplantations; these had a high success rate that was comparable with that achieved with open cross-trigonal ureteral reimplantations.[4] They placed

TABLE 1. Demographic data and operative times.

Gender	Age	Side	Grade of VUR (Lt/Rt)	Bladder capacity (mL) (mL)	Operative-time (minutes)
Male	5 yr. 2 mo.	Left	4	350	193
Female	5 yr. 10 mo.	Both	3/3	350	190
Female	5 yr. 3 mo.	Both	5/1	260	371
Male	2 yr. 4 mo.	Left	4	200	205
Male	6 yr. 1 mo.	Left	4	350	140
Female	5 yr. 7 mo.	Left	3	320	180
Female	6 yr. 5 mo.	Left	3	300	180
Male	4 yr. 3 mo.	Both	5	300	270
Male	3 yr. 1 mo.	Both	5/4	250	205
Female	4 yr. 5 mo.	Left	3	450	160
Female	3 yr. 9 mo.	Both	3/4	300	275
Male	4 yr. 11 mo.	Both	4/5	300	180
Male	1 yr. 10 mo.	Both	4/4	200	190

a camera port at the dome of the bladder instead of using transurethral endoscopy, resulting in a better forward intravesical view. Moreover, they used carbon dioxide to distend the bladder instead of glycine, which resulted in much better intravesical vision. The largest series of this technique was reported by Valla et al. in 2009.[6] Their success rate was 92%–95%, and the conversion rate was 6%. The cause of the conversions was an inability to maintain pneumovesicum, which mostly occurred in patients aged under 2 years.

From our series and experience, there are four main problems which occur during the operation. The methods to solve or to prevent those problems are described below.

Air leakage and port problem. This is an important problem that forces surgeons to convert to open surgery. Air from the inflated bladder may leak through to the urethra, the ureteral hiatus, or the port sites. The Foley catheter placement and traction can prevent air leakage through the urethra. Air leakage through the hiatus after the ureteral dissection can be solved by the immediate suturing of the defect after the ureteral dissection, and by the subsequent insertion of a small feeding tube into the prevesical space beside the ports to release the air. From the series of Mohan et al., another method to solve air leakage from the hiatus is to reduce the pressure.[7] They reduced the intravesical pressure from 14 to 8 mmHg, and air leakage did not recur. Air leakage through the port sites into the extravesical space can be prevented by anchoring the bladder to the abdominal wall and by assuring the stability of the working ports by fixing them the skin with suture material or using a balloon port instead. We observed that younger patients had a port problem more than older patients. Port displacement is also an important problem that is associated with air leakage. One patient in our series had to be converted because of severe bladder collapse from uncontrolled air leakage into the extravesical space. According to the series from Yeung et al.,[3] out of 16 patients had this problem, and 1 patient had to be converted to open surgery.[4] Canon et al. also reported a port problem.[8] One out of 52 patients in their series had to be converted to open surgery due to poor port placement and an equipment malfunction. They also reported air leakage into the peritoneal cavity, which caused pneumoperitoneum. However, transumbilical Veress needle placement was used to release the air in the abdominal cavity. In our series, no pneumoperitoneum occurred. This may be the result of using a different technique for the placement of the camera port at the dome of bladder. We used the open technique, whereas Canon et al. placed the camera port under cystoscopy. Port placement with the open technique can definitely avoid entering the peritoneum

via the peritoneal recess. In Valla's study, 4 out of 72 patients had to be converted owing to a port placement problem, and 6 patients had pneumoperitoneum, which could be corrected using a Veress needle.[6]

Bleeding. The laparoscopic approach resulted in a higher chance of serosal blood vessel preservation than the open reimplantation technique because of better visualization. However, it is possible to have a bleeding from the detrusor muscle or the serosa of the ureter during a ureteral dissection. Although bleeding in this operation is usually minimal, it will cause difficulty with the visualization of the plane between the ureter and the bladder muscle. This problem can be solved by careful electrocoagulation at the bleeding point. However, extensive electrocoagulation may cause long term complications, such as ureteral stricture due to ischemia or heat effect.

Tear of bladder mucosa over the tunnel. If this problem occurs, it can be easily corrected by suturing the tear mucosa. This problem mainly stems from an inappropriate scissor curve and working-port angle. The working ports should be placed on the Langer's line. We observed that the ureteral orifices and the interureteric bar are usually underneath the Langer's line. Consequently, we can create a submucosal tunnel in a direction that will not cause a mucosal tear. In addition, we recommend placing the working ports laterally as far as possible to make the angle of the port more parallel with the posterior bladder wall. However, one should be aware of the injury to the iliac and inferior epigastric vessels. To prevent inferior epigastric vessel injury during the working-port placement, which may result in abdominal wall bleeding or hematoma, the light from the cystoscopy shining through the abdominal wall greatly facilitates the identification of the position of these vessels.

Inability to insert the feeding tube. The feeding tube in the ureter allows us to clearly identify the contour of the ureter and the plane between the ureter and the detrusor muscle. An inability to insert the feeding tube may be caused by 2 factors: either the tube is too big, or the angulation of the ureterovesical junction is difficult. The later can be solved by inserting the guidewire first, followed by railroading the feeding tube over the guidewire. Alternatively, a smaller tube can be chosen for insertion into the ureter.

From our series, the average operative time was longer than the series of Yeung et al., Canon et al., and Valla for both the unilateral and bilateral ureteral reimplantations.[4,6,8] This may reflect the level of experience of the surgeon with laparoscopic surgery. Moreover, we found that the operative time is inversely associated with bladder capacity, with no statistical significance (Pearson correlation coefficient: -0.347; p-value: 0.25). Therefore, it would be easier for beginner surgeons to perform this operation on patients with a large bladder capacity.

CONCLUSION

Ureteral reimplantation is still a crucial operation for pediatric urologists. Pneumovesicum laparoscopic cross-trigonal ureteral reimplantation is a better option than open technique for reducing postoperative pain, the incidence of bladder spasms, and the lengths of hospital stay, and for achieving better cosmesis. Because of the many problems that may occur during the operation, this procedure may be hard to perform, but it is not impossible to learn and acquire the necessary skills. Despite there being a steep learning curve, we firmly believe that every beginner surgeon is able to carry it out effectively and safely with good outcomes.

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Outcomes and Prognostic Factors in Patients with Malignant Peripheral Nerve Sheath Tumor

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ABSTRACT

Objective: To investigate and report the clinical profiles, treatment patterns, and oncologic outcomes in malignant peripheral nerve sheath tumor (MPNST) patients, and to identify the prognostic factors that significantly affect survival.

Materials and Methods: Patients diagnosed with and treated for histologically confirmed MPNST at our institute during the January 1997 to June 2018 study period were included. Patient medical records and surgical specimens were reviewed, and study-related data was extracted and analyzed.

Results: There were 27 males and 32 females with a mean age of 44 years. Most patients presented with mass and most patients were AJCC stage III. Twenty-nine percent of patients had MPNST that was associated with NF-1. At a median follow-up time, 18 patients (30.51%) suffered from local disease recurrence. Two-year and 5-year overall survival was 72% and 46%, respectively. In univariate analysis, chemotherapy treatment and positive tumor margin were adverse prognostic factors for disease-free survival. In multivariate analysis, chemotherapy treatment (hazard ratio (HR): 3.415, 95% CI: 1.367-16.021; p=0.013) and positive tumor margin (HR: 4.680, 95% CI 1.828-10.314; p=0.014) were found to be independent prognostic factors for disease-free.

Conclusion: Chemotherapy treatment and positive tumor margin were identified as independent adverse prognostic factors for disease-free and overall survival, respectively. Accordingly, early detection and appropriate treatment are essential for improved patient outcome.

Keywords: Malignant peripheral nerve sheath tumor; MPNST; prognostic factors; outcomes; survival (Siriraj Med J 2021; 73: 763-771)

INTRODUCTION

Malignant peripheral nerve sheath tumor (MPNST) is a rare and aggressive malignant soft-tissue tumor that is characterized by high risk of local recurrence and distant metastasis.[1] There is a widely held misconception that curative treatment for MPNST is complete tumor removal, with adjuvant chemotherapy and radiotherapy recommended only in large lesions or lesions with high-grade histology.[2] Whether treatment for MPNST involves extensive surgery alone or surgery combined with adjuvant therapies, the prognosis for patients with this condition remains poor.[3] Several studies have reported 5-year overall survival rates that vary from 16% to 52%, and 5-year disease-free survival rates that range from 26% to 49%.[4-13] Neurofibromatosis type 1 (NF-1) or disease recurrence when associated with MPNST were found and reported to be adverse prognostic factors.[10,14]

The aim of this study was to investigate and report

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the clinical profiles, treatment patterns, and oncologic outcomes in MPNST patients. The secondary objective was to identify the prognostic factors that significantly affect survival.

MATERIALS AND METHODS

Seventy-one patients were diagnosed with and treated for histologically confirmed MPNST during the January 1997 to June 2018 study period. Of the 12 patients that were excluded, 3 were denied definitive operative treatment and 9 were lost to follow-up prior to 6 months after commencement of treatment. The remaining 59 patients were enrolled and included in the final analysis. After the protocol for this study was approved by the Institutional Review Board, patient medical records and surgical specimens were reviewed, and study-related data was extracted and analyzed.

A wide excision of tumor was attempted in all MPNST patients (Fig 1A-D). Radiation therapy with high-dose regimen ranging from 45 to 65 Gy was considered in patients with greater risk of recurrence based on operative and pathologic findings. There were, however, no absolute indications for radiation therapy at our center during the study period. Adjuvant chemotherapy, consisting of doxorubicin and ifosfamide, was considered in patients with high-grade disease and distant metastasis. Each patient was discussed at our weekly multidisciplinary musculoskeletal tumor board meeting to determine the most appropriate modality treatment.

Statistical analysis

Descriptive statistics were used to analyze demographic data. Cause-specific mortality, local recurrence, and distant metastasis were the clinical endpoints in this study. Data analysis were performed using statistical package Stata version 14 (StatCorp, College Station, TX, USA) and program R version 4.0.2 for windows. Shapiro-Wilk test and histogram were used to evaluate normal distribution. To summarize the data studied mean (sd) and median (range) were reported for continuous variables when appropriate, frequency and percentage for categorical variables. Kaplan-Meier method and Cox proportional hazard model was used to determine prognostic factors for two events, disease free survival and overall survival. Time to occurrence of event was calculated from the date of surgery to the date when the event occurred, or censored at the date of the last follow-up, death from other cause. Variables of interesting were gender, tumor

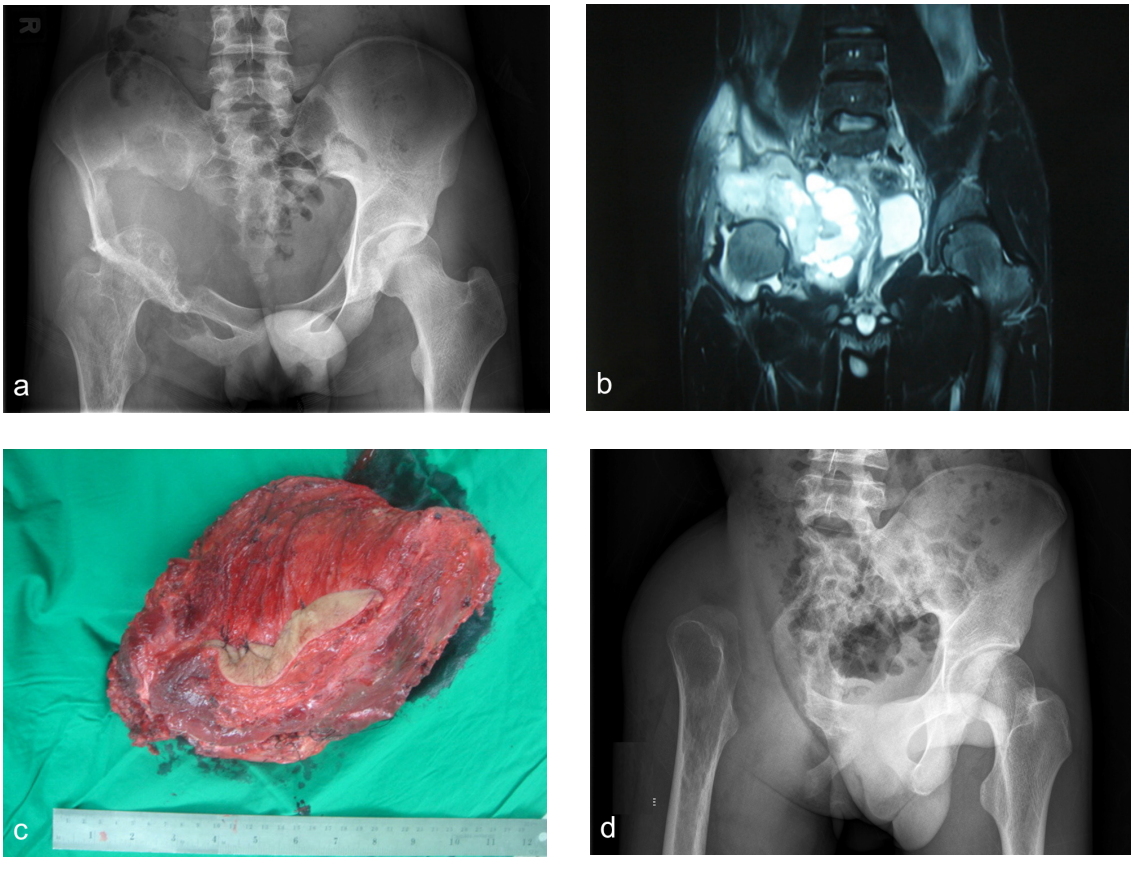

Fig 1. A 19-year-old male with MPNST with right pelvic bone destruction who underwent internal hemipelvectomy without reconstruction: **A)** Initial plain x-ray; **B)** Coronal view of T1-weighted MRI; **C)** Tumor mass after en-bloc resection; **D)** Postoperative plain x-ray

depth, NF-1, primary tumor, chemotherapy, radiotherapy, tumor site, tumor size, surgery technique, margin and severity. In this study, the variables with a univariate significance level of 0.25 or less were selected to perform multivariable Cox regression. We also included other variables from the literature which were reported clinically relevant and eligible for using in the model. Backward elimination technique was employed to select variables into the model. Proportional hazard (PH) assumption was evaluated using PH test based on Schoenfeld residuals and in survival curves plot. Variance inflation factor (VIF) was determined whether there was multi-collinearity among the variables. Candidate variables with VIF > 4 were excluded from data analysis. Goodness of fit was examined for lack of fit using graphical approach; the Cox-Snell residuals against the Nelson-Aalen cumulative hazard function plot. Data analysis was 2-tailed test with significant level 0.05.

RESULTS

The mean age at presentation was 44 years, with an age range of 13 to 86 years. Twenty-seven males and 32 females were included. Demographic and clinical characteristics of 59 study patients are shown in Table 1. Most patients presented with only one symptom (66.1%) and mass was the most frequent complaint (89.8%), followed by pain (28.8%) and neuropathy (15.3%). Twenty-one patients had been treated at other hospitals before being referred after presenting with local tumor recurrence. Most patients in this study were American Joint Committee on Cancer (AJCC) stage III (47.5%). Twenty-nine percent (17/59) of patients had MPNST that was associated with NF-1. Limb sparing surgeries could be performed in 48 patients (81.3%), with amputation required in the remaining 11 patients. Negative tumor margin could be achieved in 34 patients (57.6%), with 14 patients (23.7%) emerging from surgery with positive margins. Thirty-four patients (57.6%) received adjuvant radiation therapy, 3 patients (5.1%) received only adjuvant chemotherapy, and 11 patients (18.6%) received both adjuvant treatments.

At a median follow-up time of 48 months, 18 patients (30.5%) suffered from local recurrence of the disease. Twenty-nine patients (58%) developed metastasis, and 9 of those had multiple sites metastasis. Pulmonary metastasis was the most common site (44.1%), followed by bone, brain, and other organ at percentages of 11.9%, 3.4%, and 6.8%, respectively. Complications occurred in 15 patients (25.4%), as follows: wound dehiscence (6.8%), superficial wound infection (3.4%), phantom limb pain (5.1%). Two-year and 5-year overall survival was 72% and 46%, respectively. Median overall survival time was 58 months (Fig 2A). Median disease-free survival was 32 months based on analysis of 50 initially non-metastatic patients. Two-year and 5-year disease-free survival was 52% and 40%, respectively (Fig 2B).

Subgroup survival analysis was performed for NF-1 and type of disease presentation. Median overall survival of patients with and without NF-1 was 38 months (95% CI: 13.5-62.5) and 58 months (95% CI: 5.1-11.9), respectively, with no significant difference found between groups (p=0.648). Similarly, no significant difference was observed between patients with recurrent and primary tumor (p=0.978). Median overall survival of patients with recurrent tumor was 46 months (95% CI: 21.7-70.3), while patients with primary tumor had a median survival time of 58 months (95% CI: 0.0-121.2).

In univariate analysis in Table 2, chemotherapy treatment (hazard ratio (HR): 3.176, 95% CI 1.464-6.891; p=0.003) and positive tumor margin (hazard ratio (HR): 4.342, 95% CI 1.828-10.314; p=0.010) were shown to be adverse prognostic factors for disease-free survival (Fig 3A-B). Radiation therapy and type of surgery and AJCC stages III and IV had a non-significantly negative impact on overall survival (Table 3). Of note, AJCC staging could not be calculated as a prognostic factor for disease-free survival, because some of our patients had metastasis initially.

In multivariate analysis, only chemotherapy treatment (hazard ratio (HR): 3.415, 95% CI: 1.367-16.021; p=0.013) and positive tumor margin (hazard ratio (HR): 4.680, 95% CI 1.828-10.314; p=0.014) were found to be independent prognostic factors for disease-free and overall survival, respectively.

DISCUSSION

MPNST is widely known to be a rare and aggressive malignant soft-tissue tumor. They account for approximately 10% of all soft tissue sarcomas.[1,3] The symptoms of MPNST are non-specific. Painless mass is a common chief complaint and most patients suffer from nerve-related symptoms that are caused by tumor compression.[13,15] Our findings revealed mass to be the most common presenting symptom, while weakness and radicular pain were the least common presenting symptoms. The most widely recognized risk factor for MPNST development is NF-1, given that 10-30% of NF-1 patients will develop MPNST during their lifetime.[13] In our series, 28.8% of MPNST developed in NF-1 patients, which is comparable to the incidence reported from other studies.[4,5,11] Asavamongkolkul, *et al.* reported 2 cases of MPNST associated with NF-1, both of whom died shortly after diagnosis with distant metastases.[14] Data from survival meta-analyses reported

TABLE 1. Patient demographic and clinical characteristics.

Characteristic	Overall (n=59)	Disease free (n=50)
Gender (Female)	32 (54.2)	28 (56.0)
Mean age (year)	44	45
Follow up (months)	48 (24 – 178)*	51.5 (24 – 178)*
Number of chief complaint		
One	39 (66.1)	35 (70.0)
Two	18 (30.5)	14 (28.0)
Three	2 (3.4)	1 (2.0)
Chief complaint		
Mass	53 (89.8)	46 (92.0)
Pain	17 (28.8)	13 (26.0)
Neuropathy	9 (15.3)	5 (10.0)
Others	2 (3.4)	2 (4.0)
Presentation (Primary case)	37 (62.7)	30 (61.2)
Visit (Referred case)	45 (76.3)	38 (76.0)
Tumor site		
Neck and trunk	16 (27.1)	13 (26.0)
Extremity	42 (71.2)	36 (72.0)
Neck and Extremity	1 (1.7)	1 (2.0)
Size (More than 5 cm.)	40 (67.8)	33 (66.0)
Depth (Deep)	53 (89.8)	44 (88.0)
Grading		
Low	7 (11.9)	7 (14.0)
Intermediate	12 (20.3)	10 (20.0)
High	40 (67.8)	33 (66.0)
AJCC staging		
I	5 (8.5)	5 (11.9)
II	11 (18.6)	11 (26.2)
III	28 (47.5)	26 (61.9)
IV	7 (11.9)	0 (0.0)
Margin status		
Negative	34 (57.6)	29 (58.0)
Closed	7 (11.9)	6 (12.0)
Positive	14 (23.7)	12 (24.0)
NF-1 (Yes)	17 (28.8)	13 (26.0)
Distant metastases**	29 (58.0)	29 (58.0)
Radiation therapy (Yes)	34 (57.6)	29 (58.0)
Chemotherapy (Yes)	14 (23.7)	12 (24.0)
Dealth	24 (40.7)	

NF-1, neurofibromatosis type 1; AJCC, American Joint Committee on Cancer.
*Median (range). ** nine cases have event before begin study.

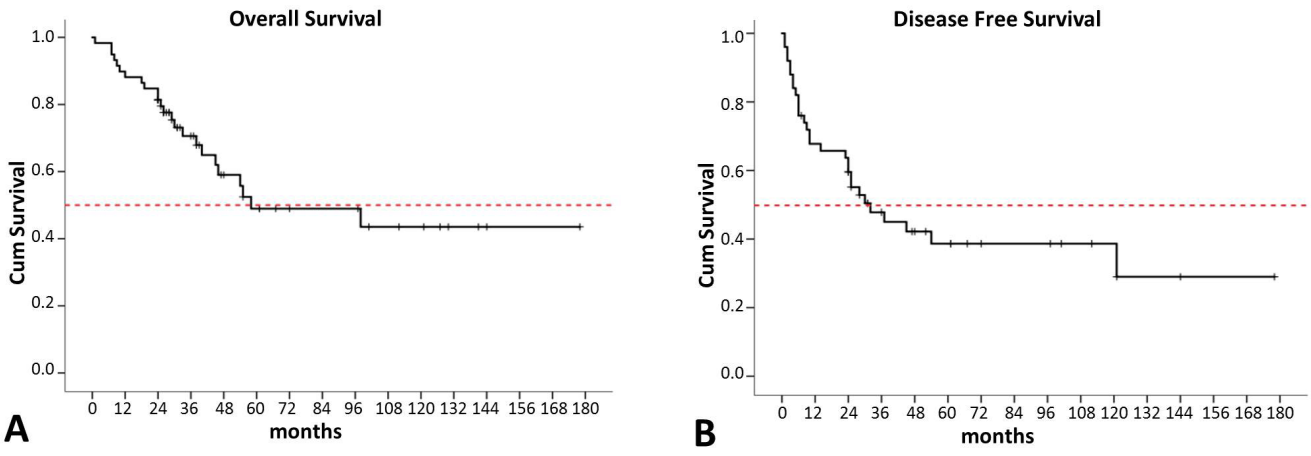

Fig 2. Survival rate of overall survival **(A)** and disease-free survival **(B)**

TABLE 2. Univariate and multivariate Cox proportional hazard regression for disease free survival (n=50).

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	p value	HR (95 % CI)	p value
Gender: (Female)	1.159 (0.551-2.435)	0.697	-	-
Tumor depth: (Deep)	1.263 (0.381-4.190)	0.702	0.552 (0.132-2.310)	0.416
NF-1: (No)	1.134 (0.459-2.799)	0.785	-	-
Presentation: (Recurrence)	1.510 (0.708-3.222)	0.286	-	-
Chemotherapy: (Yes)	3.176 (1.464-6.891)	**0.003**	3.415 (1.293-9.022)	**0.013**
Radiotherapy: (Yes)	1.548 (0.725-3.305)	0.259	0.509 (0.167-1.551)	0.235
Site: (extremity)	1.065 (0.449-2.525)	0.887	2.465 (0.862-7.049)	0.092
Size: (> 5 cm.)	1.229 (0.559-2.702)	0.608	1.136 (0.450-2.873)	0.787
Surgery: (limb salvage)	2.649 (0.791-8.866)	0.114	3.481 (0.817-14.836)	0.092
Margin*:				
Close	4.342 (1.828-10.314)	**0.010**	4.680 (1.367-16.021)	**0.014**
Negative	0.571 (0.130-2.505)	0.458	0.570 (0.120-2.718)	0.481
Grade: (High)	1.902 (0.838-4.318)	0.124	1.094 (0.408-2.930)	0.858
AJCC Staging: (III + IV)	1.468 (0.651-3.308)	0.355	-	-

* Positive qualified reference group.

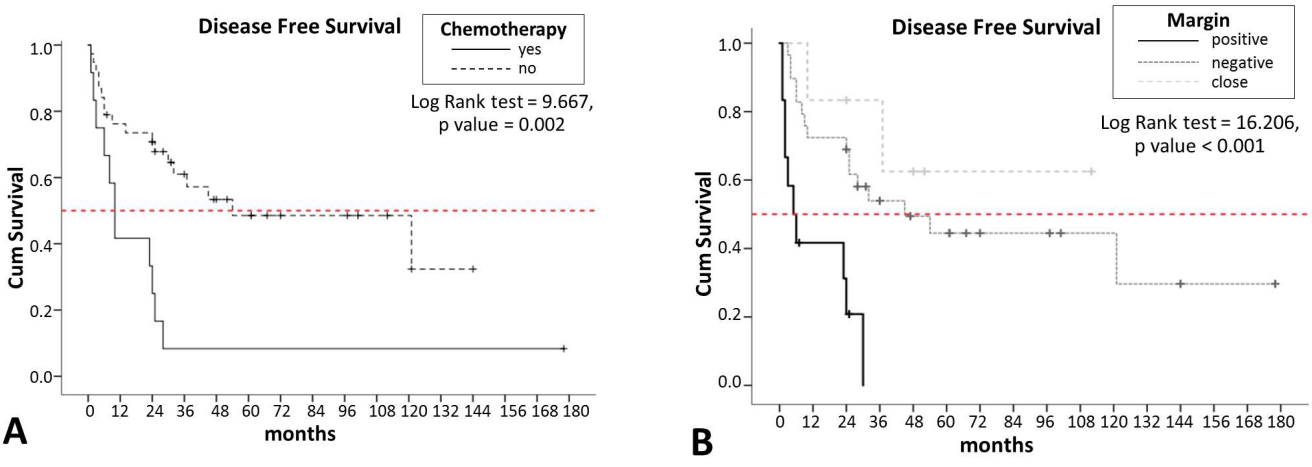

Fig 3. Disease free survival rate related to chemotherapy treatment **(A)** and tumor margin **(B)**

TABLE 3. Univariate and multivariate Cox proportional hazard regression for overall survival (n=59).

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	p value	HR (95 % CI)	p value
Gender: (Female)	1.406 (0.614-3.217)	0.420	-	-
Tumor depth: (Deep)	1.139 (0.265-4.890)	0.861	-	-
NF-1: (Yes)	1.228 (0.508-2.968)	0.648	-	-
Presentation: (Primary)	1.021 (0.442-2.317)	0.978	-	-
Chemotherapy: (Yes)	1.644 (0.699-3.867)	0.255	-	-
Radiotherapy: (Yes)	1.918 (0.793-4.638)	0.148	2.095 (0.826-5.312)	0.119
Site: (extremity)	1.152 (0.427-3.112)	0.780 (0.540-4.324)	1.528	0.425
Size: (> 5 cm.)	1.386 (0.573-3.355)	0.469 (0.631-4.370)	1.660	0.305
Surgery: (limb salvage)	1.678 (0.495-5.687)	0.406	-	-
Margin*:				
Close	1.952 (0.762-5.001)	0.164	1.669 (0.616-4.519)	0.314
Negative	0.573 (0.130-2.526)	0.462	0.474 (0.103-2.182)	0.338
Grade: (High)	2.430 (0.903-6.544)	0.079	1.799 (0.638-5.069)	0.267
AJCC Staging: (III + IV)	2.251 (0.838-6.048)	0.107	-	-

* Positive qualified reference group.

a lower odds ratio for survival in MPNST patients associated with NF-1; however, the prognosis for these patients has improved in studies published in recent years.[12]

Magnetic resonance imaging (MRI) is a valuable investigation prior to histo-pathologic study. The main objective is to differentiate MPNST from benign peripheral nerve sheath tumor using criteria that includes peripheral enhancement, mass dimension, perilesional edema, and intratumoral cystic lesion. The presence of two or more of these features is suggestive of malignancy with a specificity of 90%.[16] In contrast, target sign is also helpful in differentiating benign neurofibroma from MPNST.[17] Fluorodeoxyglucose positron emission tomography (FDG-PET) has been reported as being able to differentiate MPNST and forecast patient prognosis.[2,4]

Most patients in our series were in the advance stage – predominantly AJCC stage III (47.5%) The aggressive nature of the tumors in our study was reflected, as follows: 67.8% of tumors were high grade, 89.8% were deeply located, and 67.8% were larger than 5 cm in diameter, which was comparable to data reported from other studies.[8,10,11,13,18] The number of patients who received isolated adjuvant radiation therapy, isolated adjuvant chemotherapy, and combined adjuvant treatments was 43%, 4%, and 20%, respectively, which was comparable to data from other studies.[8-11,13] Adjuvant radiation therapy is recommended for tumors with high grade, large size, tumor recurrence, and closed margin. Alternatively, adjuvant chemotherapy is considered in tumors with high grade, large size, and metastasis. Although MPNST has relatively low sensitivity to radiation, adjuvant irradiation to doses more than 60 Gy is still associated with improved local control, but not with overall disease survival.[2,6] Carbon ion irradiation is becoming more popular due to its higher biological effectiveness compared to photons or protons, but a study in MPNST treatments revealed that it provided short-term benefits, especially in patients with gross residual or unresectable tumor.[19]

Local recurrence is common in MPNST. Incidence of recurrence ranges from 32% to 65%.[2,8-11,13] There were 18 patients (30.5%) who developed local recurrence in this study. However, we were not able to correlate recurrence with initial presentation from survival analysis.

Twenty-nine patients (50.8%) developed metastasis, and 9 of those had multiple sites metastasis. Pulmonary metastasis was the most common site (44.1%), followed by bone, brain, and other locations at percentages of 11.9%, 3.4%, and 6.8%, respectively, and these rates are comparable to rates published in other reports.[6,8-11,13] Five-year overall survival and disease-free survival in this study was 46% and 40%, respectively. Our survival rates are comparable to rates from other studies that described 5-year overall survival rates that varied from 16% to 52%, and 5-year disease-free survival rates that ranged from 26% to 49%.[4-13]

A variety of significant favorable prognostic factors have been reported from several studies. (Table 4) In the present study, chemotherapy treatment and positive tumor margin was shown to be an adverse prognostic factor for disease-free survival. Cashen, *et al*. identified Musculoskeletal Tumor Society (MSTS) Rating Scale as an adverse prognostic outcome.[7] MPNST with rhabdomyoblastic differentiation or malignant triton tumor (MTT) was reported to be associated with poor prognosis and more aggressive tumor behavior.[20] Brekke, *et al*. reported that p53-positive MPNST patients are a high-risk group and they are candidates for adjuvant treatment.[21]

Chemotherapy for soft-tissue sarcoma is limited in benefit and in variety. Chemotherapy options that include vincristine, doxorubicin, ifosfamide, and etoposide have a positive effect among metastatic MPNST patients, but not in non-metastatic patients.[22] A positive trend for adjuvant radiation, but not for chemotherapy, was observed for disease-free survival and overall survival.[13,23,24] Interestingly, we found chemotherapy treatment to be an adverse prognostic factor for disease-free survival. Targeted therapy is becoming a compelling treatment option for patients with MPNST (e.g., erlotinib, sorafenib); however, some targeted therapy studies are still ongoing and some have shown no clinical response.[2] Moreover, there are studies that have demonstrated the feasibility of anti-survivin and oncolytic measles virus as a novel treatment for MPNST patients that should be studied in future clinical trials, especially in the NF-1-related group.[25-27]

This study has some mentionable limitations. First and consistent with the retrospective nature of this study, some patient data may have been incomplete. Second, the size of the study population was relatively small. As a result, our study may have lacked sufficient power to identify all significant associations. Third, the patients enrolled in this study were from a single center, the largest tertiary referral hospital. Most patients were referred to our institute with complicated and intransigent conditions.

CONCLUSION

Patients with MPNST in this series had survival rates that are comparable to those reported in other studies. Chemotherapy treatment and positive tumor margin were identified as independent adverse prognostic

TABLE 4. Significant favorable prognostic factors.

Publications	Year	Number of cases	Significant favorable prognostic factors
Anghileri[8]	2005	205	- smaller tumor size - lack of local recurrence - extremity located
Stucky[11]	2012	175	- tumor size < 5 cm - lack of local recurrence - low histologic grade - extremity located
Zou[9]	2009	140	- tumor size < 10 cm - low intensity p53 staining
Wong[6]	1998	134	- smaller tumor size - low histologic grade - perineural histologic subtype
Lafemina[10]	2012	105	- tumor size <5 cm - low histologic grade - lack of local recurrence - extremity located
Cashen[7]	2004	80	- anatomical location - MSTS staging - lower part of lower extremity
Brekke[21]	2009	64	- tumor size < 8 cm - complete surgical resection - lower intensity p53 staining
Okada[22]	2007	56	- tumor size < 7 cm - lack of metastasis
Baehring[15]	2003	54	- tumor size < 5 cm, complete surgical resection, young age, radiation therapy, lack of chemotherapy
This study	2021	51	- lack of chemotherapy, negative tumor margin

MSTS, Musculoskeletal Tumor Society; AJCC, American Joint Committee on Cancer

factors for disease-free and overall survival, respectively. Accordingly, early detection and appropriate treatment are essential for improved patient outcome.

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Role of Laparoscopy in Diagnosis and Treatment of Endometriosis Associated with Infertility: A Prospective Analysis

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ABSTRACT

Objective: Endometriosis is often considered as an enigma due to its varied clinical presentation and challenges in diagnosis. The objective of this study is to evaluate the role of laparoscopy in diagnosis and treatment of endometriosis associated with infertility.

Materials and Methods: Infertile females diagnosed to have endometriosis during or before undergoing laparoscopic surgery from August 2018 to February 2020 were followed up for spontaneous conception for 6 months following laparoscopy. Revised American Fertility Society (r-AFS) scoring system was used to score endometriosis and stage the disease (stage I-IV). Surgical interventions were done on individual case basis following ESHRE guidelines.

Results: Fifty infertile females diagnosed with endometriosis during or before laparoscopy were recruited for the study. Mean age of patients was 28.58 (±4.21) years. Thirty-four (68%) patients had primary infertility and 16 (32%) has secondary infertility. Mean duration infertility was 3.33 (±1.43) years. Only 37 patients (74%) had evidence of endometriosis in pre-operative ultrasonography. During the follow up period of first 6 months after surgery 34 (68%) patients conceived spontaneously. Lower mean endometriosis score (p=0.00) and early stages of endometriosis (p=0.00) were associated with higher chances of conception. But, female age, duration and type infertility, USG findings and type of surgical interventions did not affect pregnancy rate.

Conclusion: Laparoscopy helps in diagnosis of endometriosis. Laparoscopic therapeutic interventions for endometriosis increase the probability of spontaneous conception in infertile females. Lower surgical score and early stages of endometriosis are associated with higher chance of conception.

Keyword: Laparoscopy; endometriosis; infertility; diagnosis (Siriraj Med J 2021; 73: 772-776)

INTRODUCTION

Endometriosis is the cause of infertility in 5-15% of women in reproductive age group.[1] It is diagnosed in 35 to 50 % of women with chronic pelvic pain, infertility or both.[2] But diagnosis is often postponed for several years after symptoms onset.[3] There is no definitive imaging modality or serum marker for the diagnosis of endometriosis. While transvaginal scan (TVS) has recently gained popularity as a first-line imaging modality for non-invasive diagnosis of endometriosis,[4] diagnostic

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laparoscopy is required for confirmation of diagnosis and staging of the disease.[5] A systematic review and meta-analysis of 13 studies on pelvic endometriosis also revealed non-invasive imaging modalities particularly transvaginal ultrasonography to be of lesser accuracy compared to laparoscopy.[6]

Excision and ablation of endometriotic lesions in mild to severe disease using laparoscopic surgery enhances fertility.[7] Surgery improves the probability of conception by restoring the anatomical distortion caused by the disease and removing the endometriotic implants, thereby reducing the inflammatory peritoneal response. Existing literature shows diversities regarding the beneficial effect of therapeutic laparoscopy in infertile females with different stages of the disease. In a retrospective cohort study, patients with severe endometriosis were followed up for natural as well as assisted conceptions.[8] Reproductive outcomes in infertile women with advanced endometriosis and repeated IVF failures were also observed.[9,10] In a retrospective study by Ekine et al. infertility patients with all stages of endometriosis were followed up for pregnancy following surgery.[11] But the pregnancies resulted from IUI and ART were also included. The current study was intended to determine the efficacy of laparoscopic surgery for diagnosis as well as treatment of pelvic endometriosis in infertile females. It observes the chances of spontaneous conception for all stages of endometriosis.

MATERIALS AND METHODS

This prospective study was carried out in a teaching hospital of Odisha, India. Institutional Ethical Committee approval was obtained for the study. For all the patients attending infertility clinic, detail history taking and relevant clinical examinations were performed. As a part of routine infertility evaluation, baseline transvaginal ultrasonography, thyroid function test and male partner's semen analysis were done. Patients with clinical and /or ultrasonographic features of endometriosis without previous history of surgery for endometriosis were planned for laparoscopy. Dysmenorrhoea, dyspareunia and chronic pelvic pain were considered as relevant symptoms for diagnosis of endometriosis. Similarly, presence of endometriotic cyst in one or both ovaries or features suggestive of utero-ovarian adhesions in transvaginal ultrasonography were presumed to be features of endometriosis. Revised AFS scoring system was used for scoring and staging endometriosis during surgery. Chromopertubation was done for all the patients. Therapeutic interventions were done as per ESHRE guidelines for endometriosis management. Complete cystectomy was preferred to partial cystectomy or cyst drainage for ovarian endometriomas. Superficial endometriotic lesions were fulgurated. Adhesiolysis was done for pelvic adhesions for restoration of tubo-ovarian relationship. Surgical specimens were sent for histopathological confirmation of endometriosis.

Patients with laparoscopic features suggestive of endometriosis were considered for the study. Females aged more than 37 years, with polycystic ovarian syndrome (PCOS) or decreased ovarian reserve were excluded. Similarly, patients with abnormal male factors and bilateral tubal block as observed during laparoscopy were also excluded from the study. Diagnosis of PCOS was done as per Rotterdam criteria. Similarly, decreased ovarian reserve was defined as antral follicle count (AFC) < 7 combined in both ovaries or anti-Mullerian hormone (AMH) < 1.1 ng/ml. Abnormal semen parameters were defined by sperm concentration < 10 million/ml and / or progressive motility < 10%.

The study subjects were followed up for 6 months post-intervention for spontaneous conception. Clinical pregnancy was considered as the outcome measure of the study. It was defined by the presence of ultrasonographic evidence of gestational sac with or without fetal pole at 7th week of amenorrhoea.

Considering the total number of patients attending infertility clinic in our hospital and the prevalence of endometriosis in infertile females, the sample size was decided to be at least 50 as this is a part of post-graduate level dissertation with a fixed duration for the study.

Data analysis

The data obtained were tabulated in Microsoft Excel. Statistical analysis was carried out with the aid of statistical programme SPSS 20.0. Quantitative data were expressed in mean and standard deviation. The percentages and proportions were used to express the categorical results. A Chi-square test was performed to compare the proportion in two groups for a categorical variable. An independent t-test was performed to look for the difference in the means of two groups with a quantitative variable, *p*-value of 0.05 was considered to be the degree of statistical significance.

RESULTS

During the study period, fifty infertile patients with endometriosis were followed up for spontaneous conception after laparoscopy. Mean age of participants was 28.5 (±4.21) years. Mean duration of infertility was 3.33 (±1.43) years. Majority of them had primary infertility (68%). Pre-Operative ultrasonography showed evidence of endometriosis only in 37 (74%) patients. Among the

patients who had ultrasonographic abnormalities, the most common finding was a right ovarian chocolate cyst (26%) followed by bilateral chocolate cysts (24%).

Intraoperatively, the minimum r-AFS score was 2 and the maximum score was 88 with mean (±SD) score of 23.76 (±19.9). Stage III endometriosis was observed in majority of these patients followed by stage I endometriosis (20%). Unilateral cystectomy was the most common intervention done in 48% of the patients, followed by bilateral cystectomy (24%) and adhesiolysis alone (12%). Other interventions were fulguration of endometriotic spots (8%), myomectomy (6%), and oophorectomy (2%).

Thirty-four patients (68%) conceived spontaneously at the end of 6 months and 16(32%) patients failed to conceive. General characteristics of these patients are compared and represented (Table 1). The mean age of patients with successful pregnancies was similar to those who failed to conceive (27.82±4.71 vs 30.18±3.35, p=0.06). Similarly, there was no difference in duration of infertility in these patients (Mean ± SD 3.35±1.45 vs 3.28±1.46, p=0.88). Among 34 patients with primary infertility, 24 (70.5%) conceived and 10 (62.5%) patients with secondary infertility conceived in the predefined postoperative period. There was, however, no statistically significant association of infertility type with the status of conception within 6 months (p=0.56).

Ultrasonographic and operative characteristics of the patients were compared and represented (Table 2). Ultrasonography findings did not affect the chances of conception (p=0.86). Majority of patients in both categories had unilateral endometriomas (15/34 vs 15/16) followed by bilateral endometriomas (9/34 vs 3/16). The mean score of endometriosis in the conceived patients was significantly lower compared to the patients who failed to conceive spontaneously (16.94±10.58 vs 38.25±26.93, p=0.00). A similar observation was also noted for stage of endometriosis. The proportion of study participants getting pregnant at the end of 6 months was higher in patients with lower stages of endometriosis than those with the higher stage (p=0.00). All the participants with stage-II endometriosis conceived and 80% with stage-I endometriosis conceived at the end of 6 months. Similarly, 76.7% of patients with stage-III endometriosis conceived but, none with stage-IV endometriosis. Out of 24 patients undergoing unilateral cystectomy, 15 (62.5%) patients conceived. Five out of 6 patients conceived where adhesiolysis was done. Successful conception was observed in all four patients after fulguration of endometriotic spots. However, there was no statistically significant association between the type of intervention done and the conception status of the study subjects (p=0.35).

DISCUSSION

In our study, 74% of patients with laparoscopically confirmed endometriosis had a preoperative diagnosis of endometriosis through transvaginal 2D ultrasonography indicating 74% sensitivity for detection of endometriosis. A similar observation was noted in a prospective study where transvaginal ultrasonography had a sensitivity of 75% for detection of endometrioma.[13] About 68% of the participants conceived spontaneously following laparoscopic intervention within 6 months. A similar spontaneous pregnancy rate (65%) was also observed in a study by Fuchs F 2007, over a follow-up period of 8.5 months. In this study, assisted conceptions were also observed.[14] The follow-up period also varied from one to two years in different studies.[15,16]

TABLE 1. Comparison of general characteristics.

Characteristics		Status of conception in 6 months		Total (n=50)	p-value
		Not Conceived n=16, (%)	Conceived n=34, (%)		
Age (Years) (Mean ± SD)		30.18 ± 3.35	27.82 ± 4.41	28.58 ± 4.21	0.06
Year of infertility (Years) (Mean ± SD)		3.28 ± 1.46	3.35 ± 1.45	3.33 ± 1.43	0.88
Infertility type	Primary	10 (29.4)	24 (70.5)	34	0.56
	Secondary	6 (37.5)	10 (62.5)	16	

TABLE 2. Comparison of USG and Operative characteristics.

Characteristics	Category	Status of conception in 6 months		Total n=50	p-value
		No Conceived n=16 (%)	Conceived n=34 (%)		
USG Findings	B/L chocolate cyst	3 (25)	9 (75)	12	0.63
	Left chocolate cyst	4 (36.4)	7 (63.6)	11	
	Myoma	1 (33.3)	2 (66.7)	3	
	No abnormality	2 (20)	8 (80)	10	
	Right chocolate cyst	5 (38.5)	8 (61.5)	13	
	Right tubo-oyarian mass,	1 (100)	0	1	
Score of endometrioses (Mean ± SD)		38.25 ± 26.93	16.94 ± 10.58	23.76 ± 19.95	0.00
Endometriosis stage	I	2 (20.0%)	8 (80.0%)	10	0.00
	II	0 (0.0%)	3 (100.0%)	3	
	III	7 (23.3%)	23 (76.7%)	30	
	IV	7 (100.0%)	0 (0.0%)	7	
Interventions done	Unilateral Cystectomy	09 (37.5%)	15 (62.5%)	24	0.35
	B/LCystectomy	5 (41.6%)	7 (58.3%)	12	
	Adhesiolysis	1 (16.6%)	5 (83.3%)	6	
	Fulguration	0 (0.0%)	4 (100%)	4	
	Myomectomy with adhesiolysis	1 (25%)	2 (75%)	3	
	Right oophorectomy with adhesiolysis	0 (0.0%)	1 (100%)	1	

Baseline characteristics of patients with and without successful spontaneous conception were similar. There was no difference in the age of females, type of infertility, duration of infertility and preoperative ultrasonographic findings making the comparison more logical and acceptable. This eliminates the probability of bias due to effect of major confounders like age on pregnancy rate.

In the present study, pregnancy rate after laparoscopy was lower in patients higher r-AFS score and advanced stages of endometriosis. This reflects the adverse effect of severity of endometriosis on the probability of spontaneous conception after therapeutic surgery. The implications of this study will help the clinicians to counsel the patients with advanced endometriosis regarding the poor prognosis for spontaneous conception following laparoscopy. It agrees with the study by Fuchs et al. 2007 where the incidence of pregnancy was significantly higher in patients with stage I /II disease than stage III/IV (89% vs 56%). In contrast, staging and scoring of endometriosis, had no association with pregnancy rate in the study by Porpora et al. 2002.[17] In that study, adnexal adhesion and tubal condition influenced the chances of conception.

The current study was undertaken at a single centre. The study followed up only cases with spontaneous conception and excluded methods of assisted reproduction as in the later cases, direct benefit of laparoscopic surgery on chances of conception would have been difficult to demonstrate. The sample size of the study was limited to only 50 patients and the follow-up duration of study participants was only 6 months which was less as compared to other studies of this nature. The limited-time period for follow-up is considered for the study as this is part

of a post-graduate dissertation that has to be completed in a limited time frame. Thus, there is a need for further studies with a larger sample size and long duration follow-up to support the observations of our study and ensure generalisability of the study for the overall population of infertile females with endometriosis.

CONCLUSION

Laparoscopy helps in the diagnosis of pelvic endometriosis especially in patients without ultrasonographic abnormalities. In infertile females with endometriosis undergoing laparoscopy, individualized surgical interventions are warranted for better fertility outcomes. Successful spontaneous conception following surgery depends on the r-AFS score, and stage of endometriosis. Lower score and early stage of endometriosis are associated with higher chances of conception.

Ethical consideration: The study was approved by the Institutional ethical committee (IEC).

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