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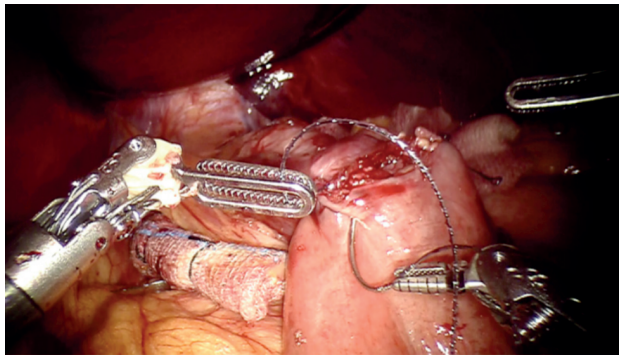

By Voraboot Taweerutchana, et al.

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An Appraisal of Totally Implantable Venous Access Devices in Pediatric Cancers

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ABSTRACT

Objective: To appraise the experience of a pediatric cancer center in Thailand regarding employment of totally implantable venous access devices (TIVAD).

Methods: The records of consecutive patients aged less than 15 years diagnosed with malignancy and underwent an implantation from the years 2010 to 2018 were reviewed with the main focus on effective duration and complications of the device. Changes in our practice in perioperative care were also reviewed.

Results: A total of 150 lines in 144 patients (103 hematologic malignancies and 41 solid tumors) were included with average age 6.4 years. Neck vein access was used in 62 lines, subclavian vein access in 88 lines. The median follow-up period was 973 days. Immediate complications occurred in 13 cases (9.4%). Excluding cases with death from unrelated causes, the overall TIVAD survival was 985.1 days while event-free device survival was 797.6 days. In cases of hematologic malignancies, which were the main users, 1000-day overall survival and event-free survival of TIVAD were 83.7% and 78.2%, respectively. Catheter-related infections and mechanical obstruction were the 2 most prevalent problems, occurring in 0.20 and 0.08 events/1,000 catheter days, respectively. Infection occurred in 23 patients and gram-negative bacilli were most common. Moreover, subclavian access was significantly related with infectious complications when compared to the neck vein approach.

Conclusion: A TIVAD can be used for chemotherapy longer than 3 years without serious complications. Refinement of surgical techniques and improving care process may improve the longevity of the line.

Keywords: Totally implantable venous access device; longevity; complications; pediatric cancer (Siriraj Med J 2020; 72: 95-102)

INTRODUCTION

A totally implantable venous access device (TIVAD) is a type of tunneled central venous catheter that provides venous system accessibility and prevents extravasation of hypertonic parenteral fluid and vesicant medications.[1] With an aim to improve quality of life (QOL) during chemotherapy[2], TIVAD are frequently used in pediatric cancer patients who require long-term intermittent therapy, especially those with hematologic malignancies.[3] TIVAD not only improves QOL, but also improves compliance to the treatment by reducing complications associated with difficult venous access.[4] Recent studies have shown that the preferred technique used in TIVAD implantation is percutaneous venipuncture, commonly via the subclavian the internal jugular vein.[5-7] If a venipuncture is not possible, open venesection is an alternative approach. Although TIVAD was designed to reduce catheter-related infections by tunneling the catheter within the subcutaneous plane,

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infectious complications can occur when the line has been used for a long period.[8,9] Moreover, mechanical complications, especially luminal obstruction, are common problems which might compromise TIVAD longevity.[10,11]

TIVAD has been practiced in Songklanagarind Hospital, one of the largest referral centers for pediatric oncology cases in southern Thailand, since 2010. After the procedure was partially subsidized by the Universal Health Coverage scheme, the number of implantations increased. The implantation was considered primarily in hematologic malignancies and in selected cases of pediatric solid tumor who were expected to receive chemotherapy for more than one year. The implantation surgical techniques and continuing post-operative care by a multidisciplinary team were continuously refined with an aim to achieve a 'best practices' program.

In this study, we appraised the longevity and the complications of TIVAD implantations in our institute and also analyzed the factors determining event-free usage longevity. Problems encountered and improvement of both surgical techniques and care processes during the period were also reviewed.

MATERIALS AND METHODS

Patient selection

The Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University approved the study as a retrospective review (EC-59-371-10-1). The records of all pediatric patients who underwent a TIVAD implantation by the pediatric surgical team at Songklanagarind Hospital from January 2010 to December 2018 and were taken care of by the pediatric oncology team either at our hospital or another hospital were reviewed.

Surgical techniques and care processes

Pediatric patients aged less than 15 years with hematologic malignancies, lymphoma, or other pediatric solid tumors were considered for TIVAD. Cases with a solid tumor were selected for implantation when they were expected to receive intermittent intravenous chemotherapy for longer than 1 year. Percutaneous venipuncture using the 'catheter under the sheath' method (Seldinger technique) was attempted first when feasible.[12,13] Puncture sites were either the right subclavian or right internal jugular vein. During the initial years of implantation in our institute, the pediatric surgeons generally preferred an approach through the right subclavian vein without ultrasonographic guidance. Around 2016, as our service quality review and other studies showed that immediate complications were lower when the internal jugular vein was used as an access point, the team revised our protocol to begin with percutaneous venipuncture through the internal jugular vein under real-time ultrasonography. In cases where a percutaneous venipuncture was not successful or not suitable, open venesection was the main alternative choice. On the open venotomy, the right external jugular or the right internal jugular was the most preferred access sites. The tip of the catheter was passed though the superior vena cava (SVC) to be located around the junction between the SVC and the right ventricle, and the location was confirmed by intraoperative fluoroscopy. (To reduce catheter misplacement as an immediate complication, strict positioning under fluoroscopy has been implemented as a quality check point since 2017.) Together with the positioning regimen, all implanted catheters were checked for their functions using 'push and pause' infusion test before fixation. The catheter was tunneled along the subcutaneous plane and the port was placed at the right chest wall cranial to the ipsilateral nipple and fixed to the pectoral fascia using 4-0 polypropylene. The skin incision was closed by a subcuticular mattress using 5-0 polydioxanone. In general, the implanted TIVAD wass left 7-10 days before the first puncture test was performed by the surgical team. The catheters thereafter were taken care of by a multidisciplinary team.[14,15] The bundles of care process were divided into 3 steps: (1) needle insertion and chemotherapy administration, (2) monthly NSS flushing to prevent mechanical obstruction, and (3) needle removal and supervised home care for the patients and their parents. The care team provided a logbook and a pamphlet to each patient's caregivers, in which events and complications were recorded. When the patients finished their intravenous chemotherapy and had no relapse of disease for at least 1 year, the device was removed by the pediatric surgical team.

As the study aimed to apprise the longevity and complications in our TIVAD practice, we also focused on the learning curve and continuous adaptation of the operative techniques through a quality assurance process of the care team. Apart from the major change in the preferential puncture site, the TIVAD clinical practice guideline has been modified several times, and the current one reflects our best practice.

Data collection

Data were retrieved from our electronic medical records including age at implantation, gender, diagnosis of malignancy, anthropometry (weight and height) at implantation, site and techniques of central venous access, size of catheter, immediate complications, type of long-term complications (catheter-related infections,

mechanical obstruction), onset of complications. Diagnosis of catheter-related blood stream infections (CRBSI) was considered when there were positive microbiological reports of hemoculture collected from both peripheral blood and catheter blood drawn at different times more than 2 hours apart[16]. Neutropenia was diagnosed when the patient had an absolute neutrophil count less than 500 cells/cm^3. Date and reasons for catheter removal were also recorded. An immediate complication was defined as an event occurring within 7 days after implantation.[17,18]

Statistical analysis

Demographic data were described by crude value and representative percentage. Categorical data were stratified by various factors and compared by chi-square test, while continuous data were compared with t-test. The log-rank test was used to calculate time to event with regard to event-free usage and overall implantation. Events per catheter day was calculated as the number of events (i.e. CRBSI, obstruction) per 1,000 overall catheter days. Statistical significance was considered at a p-value of <0.05.

RESULTS

A total of 150 devices in 144 patients (103 hematologic malignancies and 41 solid tumors) were included in the analysis. The average age of the patients was 6.4 years with 66 cases (45.8%) aged less than 5 years and 38 cases (26.4%) less than 3 years. There was an increasing trend of TIVAD use in those with hematologic malignancy when use in solid tumors gradually decreased with time (Fig 1).

Considering the access sites, neck veins were used in 62 lines and subclavian veins in 88 lines. The 26 neck-accessed lines (41.9%) were approached by an open venesection. There was a trend toward changing from subclavian access to neck vein access over the study time period (Fig 2), especially during the last years 2017-2018. Immediate complications including obstruction, displacement, arterial puncture, hydrothorax and intraoperative bleeding occurred in 13 cases (8.7%), 6 of which (46.1%) required a surgical revision (Fig 3). The median follow-up period was 973 days (interquartile range 501-1,732 days).

TABLE 1. Demographic characteristics of the patients comparing between hematologic malignancy cases and solid tumor cases.

	Hematologic malignancy	Solid tumors	Total
Patients (cases)	103	41	144
Sex			
Male	64 (62.1%)	26 (63.4%)	90 (62.5%)
Female	39 (37.9%)	15 (36.6%)	54 (37.5%)
Age (years)			
(mean ± S.D.)	6.7±3.6	5.6±5.0	6.4±4.1
Age			
> 5 years	60 (58.3%)	18 (43.9%)	78 (54.2%)
3-5 years	27 (26.2%)	1 (2.4%)	28 (19.4%)
< 3 years	16 (15.5%)	22 (53.7%)	38 (26.4%)
Weight (kg.)			
(mean ± S.D.)	23.1±12.6	21.0±19.5	22.5±14.9
Weight percentile			
<P10	17 (16.5%)	13 (31.7%)	30 (20.8%)
P10-P50	38 (36.9%)	19 (46.3%)	57 (39.6%)
P50-P90	32 (31.1%)	3 (7.3%)	35 (24.3%)
>P90	16 (15.5%)	6 (14.7%)	22 (15.3%)

Abbreviations: S.D.= standard deviation, kg.= kilograms, P= percentile

TABLE 2. Data of the 150 totally implantable venous access devices (TIVAD) used in this study.

	Hematologic malignancy	Solid tumors	Total
TIVAD (lines)	108	42	150
Insertion site			
Neck vein	43 (39.8%)	19 (45.2%)	62 (41.3%)
Subclavian vein	65 (60.2%)	23 (54.8%)	88 (58.7%)
Venous approach			
Venipuncture	94 (87.0%)	29 (69.1%)	123 (82.0%)
Venesection	14 (13.0%)	13 (30.9%)	27 (18.0%)
Immediate complications	8	5	13
Intraoperative bleeding	-	1	1
Arterial puncture	2	1	3
Displacement	4	1	5
Occlusion	1	2	3
Hydrothorax	1	-	1
Revision	5/8 (62.5%)	1/5 (20.0%)	6/13 (46.1%)
Late complications			
Infection	18 (17.5%)	5 (14.3%)	23 (16.7%)
Mechanical obstruction	6 (5.8%)	2 (5.7%)	8 (5.8%)

TABLE 3. Mechanical obstruction and catheter-related blood stream infections of TIVAD by venous access site.

Venous access site	Mechanical obstruction (events/1,000 catheter days)	Catheter-related blood stream infections (events/1,000 catheter days)
Neck vein	0.01	0.01
Subclavian vein	0.06	0.24

TABLE 4. Infectious complications in the study patients.

	Cases (n=23)	Percentage
Onset of infection		
During chemotherapy	12	52.2%
Post-chemotherapy	7	30.4%
Fever prior to admission	4	17.4%
Neutropenia	11	47.8%
Identified organism		
Acinetobacter baumannii	4	17.4%
Enterobacter cloacae	4	17.4%
Pseudomonas aeruginosa	4	17.4%
Stenotrophomonas maltophilia	3	13.1%
Staphylococcus aureus	2	8.7%
Candida albicans	2	8.7%
Cryptococcus neoformans	2	8.7%
Escherichia coli	1	4.3%
Rhodococcus equi	1	4.3%

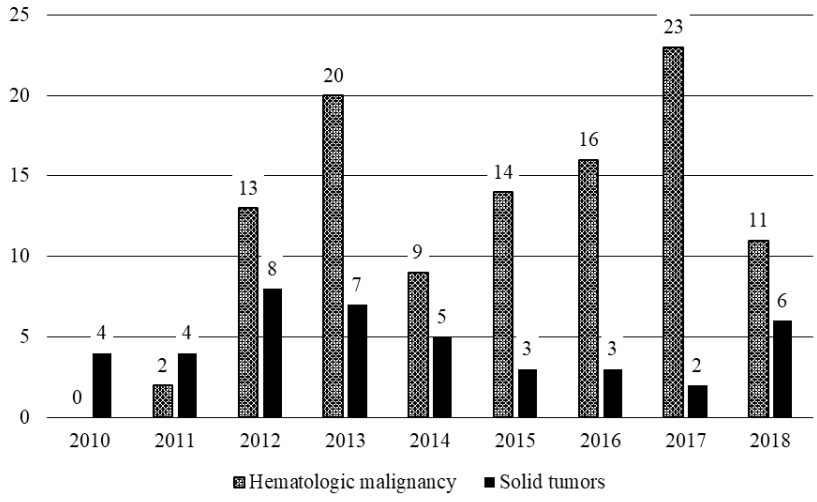

Fig 1. Total TIVAD implantation during the study period.

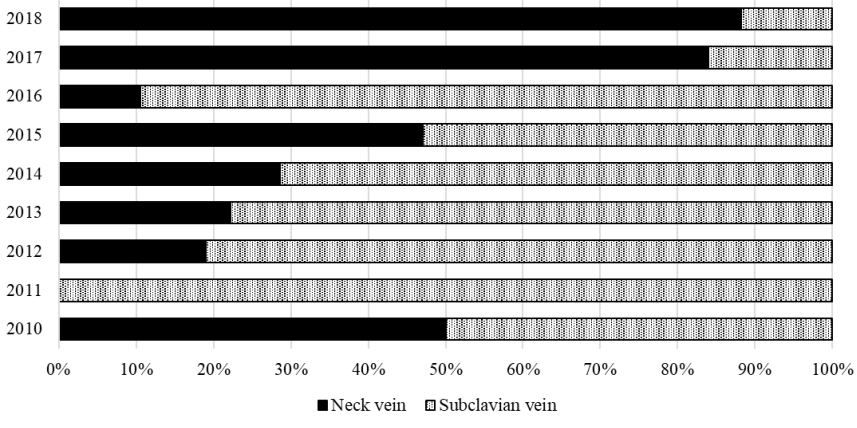

Fig 2. Site of TIVAD implantation stratified by year of implantation.

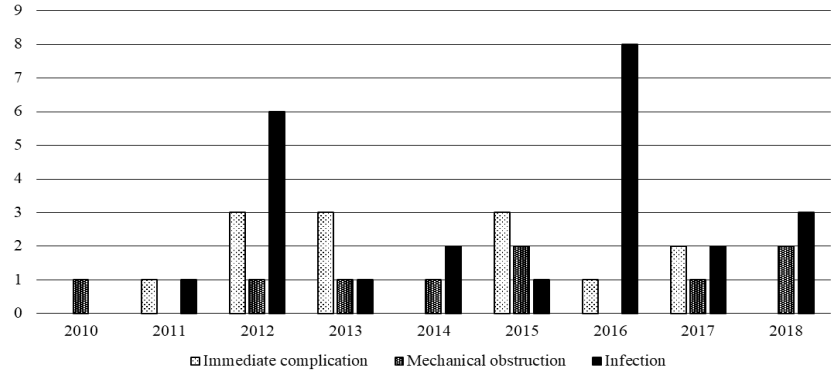

Fig 3. Immediate and long-term complications of TIVAD stratified by year of implantation.

Excluding cases with death from unrelated causes and those removed because of immediate complications, the overall TIVAD longevity was 985.1 days while event-free device longevity was 797.6 days. In cases of hematologic malignancies, 1000-day overall survival and event-free survival of TIVAD were 83.7% and 78.2%, respectively (Fig 4).

Catheter-related infections and mechanical obstruction were the 2 most common problems occurring with the device, occurring in 0.2 and 0.08 events/1,000 catheter days, respectively (Fig 5). Infectious complications occurred in 23 pediatric patients, usually developing during the chemotherapy session (52.2%) and commonly found in neutropenic condition. Gram negative bacilli was the most common organism in CRBSI (56.7%) and there were 4 cases of fungal infection. Subclavian access was related to infectious complications at a significantly higher frequency when compared to the neck vein approach (25.4% vs 9.1%, p-value 0.02). Lines with either mechanical complication or infection had significantly poorer longevity compared to uneventful implantations.

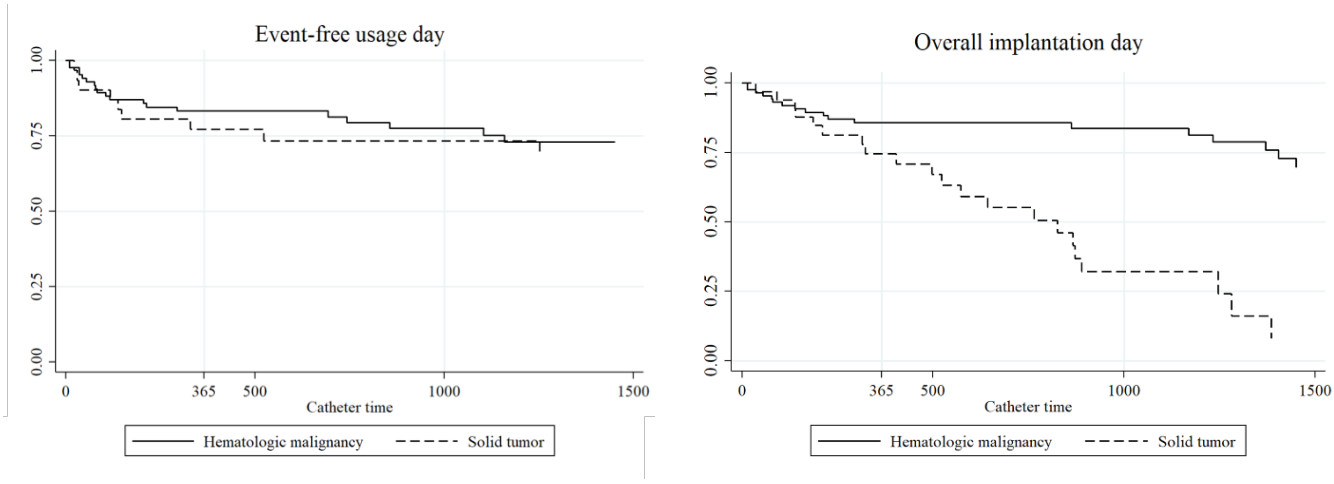

Fig 4. Kaplan Meier curves of event-free usage and overall implantation day of TIVAD stratified by type of malignancy.

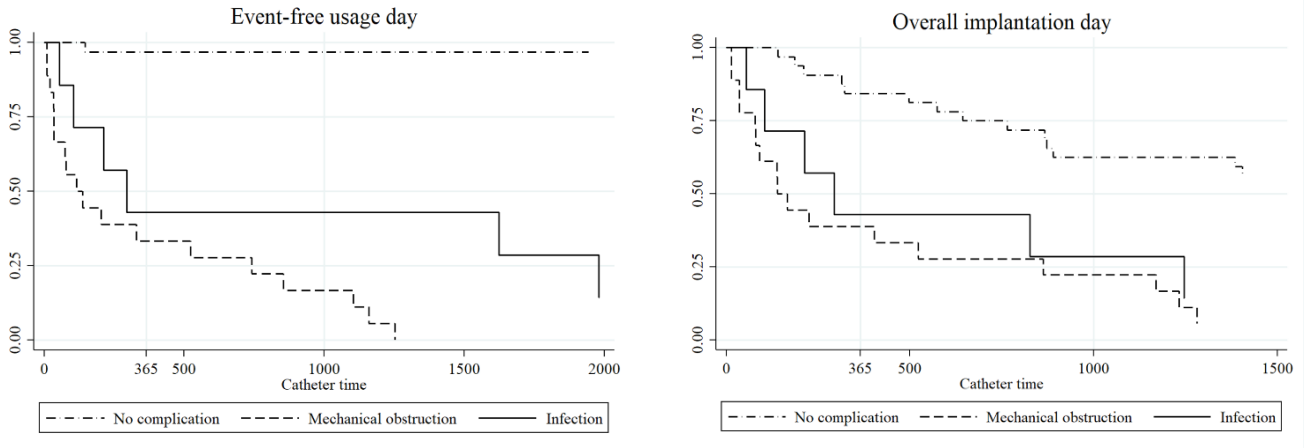

Fig 5. Kaplan Meier curves of event-free usage and overall implantation day of TIVAD stratified by type of complication.

DISCUSSION

The number of TIVAD implantations in our practice has been increasing in recent years, partly because of financial support from the Universal Health Coverage scheme of the Thailand health care system. The device is used with an aim to improve compliance with chemotherapeutic treatment by preventing extravasation and pain caused by difficult venotomies. Our study found that more than 80% of TIVAD could be used longer than 3 years. Considering its high cost, the majority of TIVAD (70%) were used primarily in hematologic malignancy cases in which the therapeutic course usually takes longer than 1-2 years. Eventually, complications developed during the period of utilization at the incidence of 0.3 events per 1,000 catheter days. The majority of complications were related to mechanical obstruction and catheter-related blood stream infections (CRBSI). There were 2-time peaks of complication occurrence, the first being immediate complications that occurred within days of implantation in which mechanical problems predominated and the second being infectious complications during the first year of catheter use. This high complication occurrence during the first year of use might be explained by the intensity of chemotherapy in that period. Our data also found that once a complication occurred, the longevity of the TIVAD was significantly compromised.

The TIVAD is a catheter of which the whole device is surgically implanted within the body, one end laid in the vena cava and the other end placed under the skin. Although this system has been proven to have less chance of infection when compared to the exteriorized catheter, CRBSI remain a concern. During the on-going period of this study, we found that the neck vein approach was superior to the subclavian approach in terms of a significantly lower incidence of CRBSI[7,19], and based on this finding we modified our surgical protocol to perform internal jugular venous puncture under ultrasonographic guidance as the first choice. Now in our institution the use of fluoroscopy and flow check before the end of a TIVAD procedure are mandatory. With that strategy

launched in 2017, the immediate complication rate reduced from 11% to 6% of total implantations and there were no immediate complications in 2018.

Risk reduction in TIVAD implantation and care involves not only the surgery and post-surgical care but also patient preparation and right surgical timing.[20] One lesson our team has learned in our early experience is that implantation should be avoided during the period that a patient remains in blast crisis or the bone marrow suppression phase. Implantation is scheduled when a leukemic patient enters a remission phase and his/her hematologic profile is within the normal range, usually between the first and second sessions of chemotherapy. Even though transfusion therapy might be able to quickly restore the number of platelet count to the normal limit, the risk of hemorrhagic complications and soft tissue infection are not substantially alleviated[21]. Concerning post-operative and long-term care, a multidisciplinary team approach is the key point[14]. The first puncture of a device is usually performed by the pediatric surgical team. Further maintenance is then in the hands of pediatricians and chemotherapeutic nurses in the pediatric cancer ward. Such care includes a log-book record and regular inspection and irrigation. With refinement of surgical techniques, the complication rate in our institution gradually decreased from 29.6/100 catheters to 15.6/100 catheters after the year 2017.[15]

Our next aim to improve the effective use of TIVAD is to reduce infectious complications. Our data showed that half of the CRBSI occur during the chemotherapeutic session. During the neutropenic period, even though a double culture technique was used, it was not easy to differentiate between systemic bacteremia and primary catheter infection. When blood culture is positive with gram negative bacteria or fungus, removal of the device is usually inevitable. Active surveillance of bacterial colonization within the device and avoiding its use during the neutropenic period may reduce the problems.

CONCLUSION

In conclusion, our study documents the continuous improvement of our practice in TIVAD implantation and care in pediatric malignancy cases. Over time, continually improving surgical techniques and multidisciplinary care reduced complications and improved longevity of TIVAD implantation.

Conflict of Interest: All authors have no conflict of interest

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Incidental Malignant Lymphoma and Lymphoproliferative Disorders in Lymph Node Dissection Specimens during Tumor Removal in Various Organs

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ABSTRACT

Objective: To find incidental malignant lymphoma and lymphoproliferative disorders (LPD) in lymph node dissection specimens during tumor removal in various organs.

Methods: A review was performed separately by two pathologists in two rounds of all H&E-stained slides of lymph nodes found during the removal of solid tumors at Siriraj Hospital: the first round concentrating on the detection of any metastatic tumor cells in lymph node sinuses and the second round concentrating on any incidental lymphoma or LPD. Then, the results were compared to reach consensus. Immunohistochemical studies were performed to help confirm the diagnosis of lymphoma or LPD.

Results: In total, 309 cases were reviewed. Lymph nodes were taken out during surgical tumor removal of the breast (110 cases), colon and rectum (57 cases), female genital organs (41 cases), lung (20 cases), thyroid (20 cases), oral cavity (16 cases), prostate (14 cases), and others (31 cases). Only 1 case (0.3%) was found to have follicular lymphoma, while 4 cases (1.3%) were found to have LPD, including in situ follicular neoplasia (1 case), suspected follicular lymphoma (1 case), and marginal zone hyperplasia (2 cases). An experienced pathologist was able to detect incidental lymphoma and LPD.

Conclusion: Incidental lymphoma and LPD can be found in lymph node dissection specimens. Attention should thus be paid during histologic evaluation to find any incidental lymphoma or LPD for another round of lymph node screening after finishing the search for metastasis in the lymph node dissection or sentinel lymph node biopsy to avoid "inattentional blindness."

Keywords: Incidental lymphoma; lymphoproliferative disorders; lymph node dissection; solid tumor; inattentional blindness (Siriraj Med J 2020; 72: 103-108)

INTRODUCTION

Based on research conducted on malignant lymphoma at Siriraj Hospital in the past decades, one of the authors (SS) has been publishing pathologic data regarding malignant lymphoma in Thai people in international medical journals since 1998.[1] Moreover, the same author published a report in an international medical journal in 2004 on malignant lymphoma types in Thai people

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diagnosed from this single institution in up to 1,983 cases.[2] Further studies have been periodically published regarding various aspects of malignant lymphoma in Thai people.[3-10] Interestingly, the information from Siriraj Hospital on malignant lymphoma in Thai people is comparable to the data reported from a later collaborative study of malignant lymphoma in Thai people among many medical centers in Thailand,[11] which is perhaps not surprising as Siriraj Hospital is the largest government-based hospital (2,000 in-patient beds) in Thailand and is equipped with its own pathology laboratory, rendering the institute higher chances of obtaining pathology specimens and encountering a wider range of malignant lymphoma than in smaller hospitals. Furthermore, the existence of a great number of patients with long follow-up visits allows an appreciation of disease variations along the clinical course or any related conditions or emerging morbidities. Also it is possible to note incipient lesions encountered in previous pathology specimens taken from the patients before they developed overt lymphoma. Recently, the same author (SS) has published the results of the study on "Pathologic findings prior to the diagnosis of malignant lymphoma – a retrospective study in a large medical institute" based on a review of all previous pathology slides prior to the definite diagnosis of malignant lymphoma, with an aim to search for any lymphoma or lymphoproliferative disorder that might have been missed in the initial diagnosis. Among the 999 lymphoma patients who made at least one visit to Siriraj Hospital for a definite diagnosis or follow-up, there were two lymphoma patients who had a previous history of cancer, one with a lobectomy for lung cancer and the other with mastectomy for breast cancer. Upon reviewing the lymph node dissection slides on these two patients, it was found that both had already had lymphoma in those lymph nodes but they were missed by the original pathologists: one a case of diffuse large B-cell lymphoma (DLBCL), where the pathologist had failed to recognize a small cell lymphoid neoplasm in the regional lymph nodes in the resection specimen of pulmonary adenocarcinoma 1 year earlier, and another case of follicular lymphoma (FL) in the sentinel lymph node in a patient with CA breast 4 years earlier.[12] These missed diagnoses can be explained by the perceptional phenomenon described as "inattentional blindness";[13] whereby the attention of the pathologist at the time was only on the metastatic tumor cells, mostly confined in lymph node sinuses, while the other portions of the lymph node were neglected (overlooked or "blind"). So the lymphoma was not reported at that time.[12]

After the aforementioned study, 4 more cases were found during hematopathology services at Siriraj Hospital by one of the authors (SS), namely: 1) a newly diagnosed case of chronic lymphocytic leukemia (CLL) found to have already had small lymphocytic lymphoma (SLL) in the lymph node dissection specimen taken for prostatic adenocarcinoma performed 6 years previously, but missed by the attending pathologist at that time; 2) a case of CLL proven to have nasopharyngeal involvement by tissue biopsy, which also had the involvement of all the lymph nodes in the lymph node dissection specimen taken for pulmonary adenocarcinoma in the following few months, but was missed by the attending pathologist at the time (the surgeon failed to inform the underlying CLL to the pathologist); 3) a case of mantle cell lymphoma (MCL) with the involvement of all the lymph nodes of a lymph node dissection specimen taken for pulmonary adenocarcinoma several months later, but was initially missed by the attending pathologist; and 4) a known case of rectosigmoid adenocarcinoma that had follow-up colonoscopy 2 years later and was found to have multiple polyps. The polypectomy specimen was shown to have extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma). Then, a review of the previous surgical removal of the rectosigmoid adenocarcinoma revealed that the lymph nodes involved marginal zone lymphoma but no MALT lymphoma was detected in any colonic mucosa taken for histologic evaluation. No polyp was found in the resection specimen at that time.

These incidental lymphoma cases prompted the authors of the present study to review the literature, which revealed that the frequency of incidental lymphoma in lymph node dissection ranged from 0.2% to 1.6% of cancer patients who underwent tumor removal.[14-20] Most previous studies were conducted in prostatic cancer patients (0.2–0.4%),[14-17] and only three studies were conducted in melanoma patients (0.3%),[18] head & neck cancer patients of the squamous cell carcinoma type (1.5%),[19] and breast cancer patients (1.6%).[20] Given this possible incidence reported in the literature, it would be interesting to know whether lymph node dissection in cancer patients performed at Siriraj Hospital could result in any chance of missed incidental lymphoma or lymphoproliferative disorders (LPD).

MATERIALS AND METHODS

The pathologic diagnosis of lymphoma given in this study followed the WHO classification based on clinical, morphologic, immunophenotypic, and genetic findings.[21]

Nevertheless, due to some limitations, especially in genetic studies, the diagnoses in this study were given primarily based on the morphologic and immunophenotypic findings. Table 1 shows the list of antibodies for the lymphoid markers used for immunohistochemistry in the present study.

After receiving a certificate of approval for this study from the Siriraj Institutional Review Board (Si 289/2018), a search of the laboratory information system used at Siriraj Hospital, known as "HCLAB", was conducted by one of the authors (SS) only. All the slides available in the archive room were retrieved. After that, both authors (SS and WMO) independently performed histologic reviews of the slides without any communication between them. They performed their reviews in two rounds: the first round concentrated on the detection of any metastatic tumor cells in lymph node sinuses, while the second round concentrated on the lymph node changes to detect any incidental lymphoma or LPD. After both authors had finished their pathology reviews independently, a comparison of the results was performed to reach consensus.

RESULTS

The project had to be completed within a one-year training period to fit in with a hematopathology fellowship program followed by one of the authors (WMO) under the tutelage of the other author (SS). Due to the time constraint, only 309 cases in total could be reviewed. The demographic data are summarized as follows: female to male ratio, 2.5 (221 to 88); ages of the patients, 21 to 91 years old (median, 60 years old; mean, 59.7 years old); organs with tumor removal: the breast (110 cases), colon and rectum (57 cases), female genital organs (41 cases, including the uterus in 25 cases, ovary in 11 cases, and uterine cervix in 5 cases), lung (20 cases), thyroid (20 cases), oral cavity (16 cases), prostate (14 cases), larynx (8 cases), skin (5 cases), stomach (5 cases), liver (4 cases), pancreas (3 cases), kidney (3 cases), tonsil (1 case), small intestine (1 case), and eyeball (1 case).

There were 5 cases found of incidental lymphoma and lymphoproliferative disorders in lymph node dissection specimens during tumor removal. The results are presented in Table 2. There was 1 case of follicular lymphoma (FL) at the time of first diagnosis of endometrial carcinoma by the original pathologist. Here, the reviews by the two authors concurred with the diagnosis of crowded neoplastic lymphoid follicles with the BCL2+, CD10+, and CD20+ phenotypes typically seen in FL. This patient was a 55-year-old female, who was lost to follow-up following discharge after surgical tumor removal, so the hematologic work-up for a complete clinical staging was lacking. Then there were 4 cases recognized to be abnormal by the experienced hematopathologist (SS) only: 2 suspicious of FL and 2 suspicious of small cell lymphoid neoplasm (SCLN) with a mantle/marginal zone configuration. Immunostaining showed that 1 of the 2 suspected cases of FL turned out to be *in situ*

TABLE 1. List of antibodies for lymphoid markers used for immunohistochemistry in the present study.

Antibody to	Marker for	Remarks
CD3	T-cells	Common T-cell marker
CD5	T-cells	Aberrant expression in B-cell neoplasms
CD10	B-cells & T-cells	Germinal center B-cell & T follicular helper
CD20	B-cells	Common B-cell marker
CD23	B-cells & FDC	FDC meshwork in reactive germinal center
Cyclin D1	Cell cycle protein	Expressed in neoplastic mantle cells
BCL2	Anti-apoptotic protein	Expressed in neoplastic germinal center cells and various types of lymphomas
Kappa light chain	Ig, light chain	Expressed in some plasma cells
Lambda light chain	Ig, light chain	Expressed in some plasma cells
IgD	Ig, delta heavy chain	Expressed by naive B-cells in mantle layer

Abbreviations: FDC: follicular dendritic cells; Ig: Immunoglobulin

TABLE 2. Incidental lymphoma and lymphoproliferative disorders in lymph node dissection specimens during tumor removal (total of 5 cases).

Case (age/sex)	Tumor removal	Incidental lymphoma/LPD	Recognized by
#1 (55/F)	Endometrial carcinoma	Follicular lymphoma, low grade	Original pathologist, SS, WMO
#2 (74/F)	invasive ductal carcinoma of breast	In situ follicular neoplasia	SS only
#3 (68/M)	CA rectum	Suspected follicular lymphoma	SS only
#4 (67/F)	Endometrial carcinoma	Marginal zone hyperplasia	SS only
#5 (80/F)	Endometrial carcinoma	Marginal zone hyperplasia	SS only

Note: There was no metastatic carcinoma in any of the lymph nodes in these 5 cases.
Abbreviations: SS: Sanya Sukpanichnant; WMO: Win Myat Oo

follicular neoplasia (but this was still queried as low grade FL) as shown by the few BCL2+, CD10+, and CD20+ neoplastic lymphoid follicles located close to one another, but not typically as crowded as those found in FL. This patient was a 74-year-old female who had invasive ductal carcinoma of the breast. The other suspected case of FL failed to show any BCL2 protein expression, even when using 2 clones of antibodies for BCL2 (clone 124 and clone E17) in the crowded lymphoid follicles. The 2 suspected cases of SCLN with a mantle/marginal zone configuration were pelvic lymph nodes that had hyalinized vessels. They turned out to be marginal zone hyperplasia (MZH) after immunostaining with the help of IgD to separate the lymphoid cells in the mantle layer from the lymphoid cells in the MZH. Both patients, aged 67 and 80 years old, respectively, were diagnosed as endometrial carcinoma. All of these 4 abnormal cases did not have any further submission of a pathological sample after surgical tumor removal up to the time of the manuscript preparation on August 23, 2019. In all these 5 cases in Table 2, there was no evidence detected of metastatic carcinoma in the lymph node.

In summary, only 1 out of 309 cases was proven to have low grade FL (0.3%). The other 2 cases of suspected FL were proven to be *in situ* follicular neoplasia (1 case) and a still questionable case of FL (1 case). The other 2 cases of suspected SCLN were proven to be MZH. If these 4 cases are considered as LPD, then the incidence of incidental LPD was 1.3%.

DISCUSSION

Incidental lymphoma and LPD can be found in lymph node dissection specimens during tumor removal in various organs, as shown in the results above. From the present study, incidental lymphoma was found in 0.3% of the 309 cases evaluated, which is an incidence not different from those reported in the literature.[14-20] However, its early recognition is important, leading either to hematologic work-up for a complete clinical staging when the incidental lymphoma is established or to searching for a definite lymphoma diagnosis when incidental LPD is found. Most of the incidental lymphoma cases reported in the literature and in this study have been indolent lymphomas without any systemic symptoms, such as SLL/CLL, follicular lymphoma, or marginal zone lymphoma.[14-20] Since the conventional management in asymptomatic indolent lymphoma is usually to adopt a "watch and wait" policy,[22] it seems that incidental lymphoma found in lymph node dissection specimens during tumor removal in various organs may not be an issue of concern in terms of clinical significance. But, in fact, it does matter, as large cell transformations can occur in a number of indolent lymphoma patients.[23] In our experience and as already published, one case of DLBCL involved a failure to recognize small cell lymphoid neoplasm (SCLN) in the regional lymph nodes in the resection specimen of a patient with pulmonary adenocarcinoma 1 year earlier.[12] It would have been much better if the indolent lymphoma (SCLN) was recognized at the time of CA lung resection and the patient had undergone hematologic work-up for a complete clinical staging and proper management, including follow-up. The problem found in these patients after surgical tumor removal is a loss of adequate follow-up as the patients may believe that they are cured; for instance, all 5 patients in the study shown in Table 2 did not have any further

submission of a pathological sample after surgical tumor removal.

According to the WHO classification (revised 4th edition, 2017),[21] "*in situ* follicular neoplasia (ISFN)" is defined as partial or total colonization of germinal centers by clonal B-cells carrying the *BCL2* translocation characteristic of follicular lymphoma (FL) in an otherwise reactive lymph node. For patients with incidentally diagnosed ISFN and no other evidence of FL upon clinical evaluation, the risk of subsequent FL is very low (≤ 5%). By morphology alone, it is difficult to recognize ISFN, and the affected follicles composed almost exclusively of centrocytes (closely packed centrocytes) may be the only histologic clue for ISFN. Certainly, immunohistochemistry for BCL2 and CD10 will show BCL2+ centrocytes exclusively in the affected follicles, with a higher intensity than in adjacent T-cells or cells in the mantle layer. These BCL2+ centrocytes will also show an increased expression of CD10. Thus, according to the aforementioned findings, ISFN could be diagnosed without the need for genetic studies to confirm the diagnosis. But, if any genetic profiles are needed, ISFN cells are positive for t(14;18) or mutations in *EZH2*.

For the other case of "suspected follicular lymphoma (FL)," the morphology was quite typical for FL, but in this particular case, the lymphoma cells lacked the expression of the BCL2 protein, even when using the 2 clones of antibodies for BCL2 (clone 124 and clone E17). This phenomenon is at times seen in daily practice and it can happen when secondary events lead to mutations in *BCL2*, resulting in a negative staining of FL with the commonly used clone 124 antibody to BCL2. According to the WHO classification,[21] the absence of BCL2 protein does not exclude the diagnosis of FL. Other germinal center markers, including LMO2, GCET1, and HGAL, will be positive in these cases. Determination of surface immunoglobulin (sIg) by flow cytometry can be helpful to establish evidence of neoplastic follicular center cells. However, in this study, this particular case of "suspected FL" did not have confirmation done by using any other germinal center markers or the determination of sIg by flow cytometry because the morphology and the CD10+ and BCL6+ phenotypes in the lymphoma cells seemed to be sufficient to designate this case as "suspected FL."

Regarding the 2 cases of marginal zone hyperplasia (MZH) in the study, the literature emphasizes excluding MZH before making a diagnosis of nodal marginal zone lymphoma (NMZL). The identification of three separate zones, namely the innermost pale zone of the reactive germinal center, the dark staining mid zone of the mantle layer, and the outermost pale zone of the marginal zone, without distortion of other lymph node compartments or pericapsular infiltration should lead to a concern of MZH. The B-cells in MZH are frequently negative for BCL2 and CD43. Plasma cells should be polyclonal in MZH. In case of doubt, flow cytometry or a molecular study for the clonal rearrangement of the immunoglobulin heavy chain gene would be helpful to distinguish MZH from NMZL. MZH should lack monoclonal evidence.[24,25] Since MZH of the lymph node is rare, it is quite difficult to find the causes. However, the following causes have been described in the literature: *Haemophilus influenzae* infection (6 cases),[26] EBV infection (1 case),[27] and systemic bacterial infection (1 case).[28] In addition, associated conditions found at the time of lymph node swelling were chronic tonsillitis (1 case) and hepatocellular carcinoma (1 case).[24]

The present study does support the "inattentional blindness" phenomenon[13] as attention was only on the metastatic tumor cells, mostly confined in lymph node sinuses, while the other portions of the lymph node were neglected (overlooked or "blind") as proposed by one of the authors (SS).[12] Also it was observed in the study that recognition of the histologic findings of various types of lymphoma and LPD plays an important role in enabling pathologists to suspect incidental lymphoma or LPD in lymph node dissection specimens during tumor removal in various organs. In order to overcome the "inattentional blindness" phenomenon during histologic evaluation of lymph node dissection specimens during tumor removal in various organs, it is recommended that pathologists look at all histologic sections of the lymph nodes in a second round for any incidental lymphoma or LPD after searching for metastatic tumor in the first round. Certainly, improving the recognition of the histologic findings of various types of lymphoma and LPD by an individual pathologist may be difficult to achieve as it is personal capability, but continuing education may enhance this capability.

CONCLUSION

Despite the low incidence of incidental lymphoma, it is more beneficial for patients if pathologists can detect lymphoma in the lymph node dissection during the surgical removal of solid tumors. The findings from the present study raise some suggestions on ways to enhance the detection of incidental lymphoma, including: 1) paying specific attention to be able to find any incidental lymphoma in a second round of lymph node screening after finishing the search for metastasis in the lymph node dissection or sentinel lymph node biopsy in a first round, in order to avoid "inattentional blindness;[13] and

2) having a greater awareness of the morphology features in lymphoma and LPD. The latter requires more interest in hematopathology among general pathologists, as experienced hematopathologists may already be aware of more varieties in lymphoma and LPD during screening.

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Effectiveness of Back Exercise and Education for Lower Back Pain Prevention among Nurses at a Tertiary Hospital in Bangkok, Thailand

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ABSTRACT

Objective: To examine the effectiveness of back exercise and education to promote lower back pain relief among nurses at a tertiary hospital.

Methods: This quasi-experimental study was conducted using a sample of sixty nurses working at Siriraj Hospital. Eligible criteria included full-time registered or practical nurses who had undergone direct contacted with patients for at least six months and suffered from chronic lower back pain. The subjects were randomly divided into a training group and a control group. The training group followed a back exercise program including pelvic tilting, back extension, and knee to chest at least 3 days a week for 12 weeks while the control group performed daily activities as normal. Data were collected using a questionnaire at baseline, 4th, 8th, and 12th weeks.

Results: Significant differences of pain score and the Thai version of the Oswestry questionnaire were scored between the training and control groups (*P-value* < *0.001*), while beneficial effects improved significantly during the time points of exercise (*P-value* < *0.001*).

Conclusion: Back exercises and education can effectively relieve lower back pain and improve disabilities among nursing staff. Following our recommended procedures will improve the safety aspect for nurses working in tertiary hospitals.

Keywords: Lower back pain; back exercise; nurse (Siriraj Med J 2020; 72: 109-116)

INTRODUCTION

Lower back pain (LBP) is considered to be a major health problem among occupational diseases[1] and is usually found in musculoskeletal disorders (MSDs).[2] LBP is the leading cause of disability in daily life.

People with chronic LBP (CLBP) show muscle weakness and atrophy predominantly in the lumbar flexors and extensors due to deterioration of the multifidus muscle. Advanced symptoms are associated with reduced muscle size presenting a smaller cross-sectional area, leading to a decrease in muscle endurance, flexibility and back motion.

Trunk muscle strength protects the spine during activities.[3-5] Many previous studies indicated that exercise

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improved the strength, endurance, and flexibility of back muscles with also a positive impact on pain levels. Results demonstrated that healthy participants had more muscular strength and endurance than those with LBP.[6] However, some evidence suggested that only exercise or exercise together with education were effective for LBP prevention, while education alone was unlikely to result in any improvement in LBP.[7-9]

Incidence of LBP was 26.4% for people over 45 years of age as the top health problem in the USA.[10] In Thailand, the Division of Occupational Health, Ministry of Public Health found that approximately 79% of the study population had MSDs related to occupation and LBP was found in 52.4% of the subjects.[1]

Nursing is an occupation with a high risk of LBP related to the working environment. In Thailand, 65-84% of nurses suffer from LBP as a result of lifting or moving patients incorrectly, prolonged standing or sitting while working, improper working posture, lack of exercise and wearing high-heeled shoes.[1,11,12] Thus, nursing personnel require protection by reducing spinal health hazards. Siriraj Hospital is one of the tertiary hospitals in Bangkok where many nurses are working at risk. Policymaking should involve hospital assurance, risk management and health promotion and prevention schemes to address how to prevent employees from incurring serious and long-term injuries related to daily working operations. Education and back exercises are routinely included in musculoskeletal clinics for LBP management; however, the outcomes are equivocal with no evidence suggesting that one particular type of exercise therapy is clearly more effective than others.[13-16] Moreover, various exercises are prescribed randomly and no single standard of care is recommended. Clinical and biomechanical approaches for the prevention of LBP tend to follow the favorite exercises and beliefs of individual therapists. In this study, a simple and common back exercise program was selected, combined with the education necessary for members of the nursing staff suffering from mechanical back pain without any specific cause. The objective was to examine the effectiveness of education and exercise for LBP relief among nurses. The hypothesis was postulated that exercise could reverse neuromuscular impairment of back muscles and improve lower back pain. Education greatly improves self-awareness and self-protection, while behavioral change can result from exercise compliance. If proved effective, implementation of a combined exercise/education scheme could improve safety for nurses operating in the workplace.

MATERIALS AND METHODS

This quasi-experimental study was approved by the Institutional Review Board, Faculty of Medicine Siriraj Hospital (Si 377/2016). The sample size was calculated using the mean pain score from a previous study[17] and adding 25% to allow for missing data. The required sample size of subjects was sixty. Type I error was set at 0.05 and the power of the test was set at 0.80.

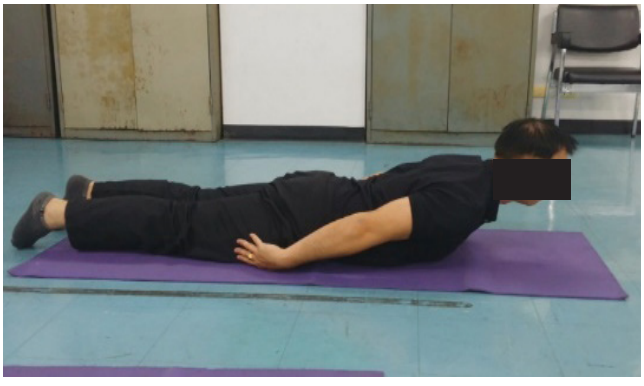
Nurses working at Siriraj Hospital were recruited and selected based on eligible criteria. The samples were randomly divided into training and control groups. As inclusion criteria, the subjected were required to be registered or practical nurses, working full time in the same ward, with direct contact with patients for at least 6 months and suffering from chronic LBP (pain duration >3 months). Pregnant nurses and those with chronic LBP with specific pathology e.g. disc herniation, spondylolisthesis, LBP with red flag signs and symptoms, concomitant treatments such as other physiotherapy like TENS, heat modalities, analgesics, acupuncture, spine surgery, etc. or staff members unwilling to participate in the exercise were excluded.

Data were collected using a questionnaire comprising demographic characteristics, occupational information, pain score, and the Thai version of the Oswestry questionnaire score. Pain score was evaluated as a psychometric response by a visual analog scale (VAS). A score of 0 corresponded to no pain and a score of 10 indicated the most pain. Correlation between the vertical and horizontal orientations of the VAS was 0.99.[18] The Thai version of the Oswestry questionnaire score was used to evaluate the functional disability. Cronbach's alpha coefficient of reliability was 0.91.[19]

The training group participated in the exercise program which was led by sports scientists from the Department of Health Promotion for at least 3 days a week for 12 weeks, while the control group performed daily activities as normal. Exercises included pelvic tilting related to core stabilization, back extension to strengthen back muscles and possibly benefit lumbar disc bulging or protrusion, and knee to chest to promote lower back and gluteal muscle stretching and flexibility as shown in Fig 1 (a-c).[20-22] Furthermore, all participants were educated regarding the definition of LBP, risk factors, and early warning signs and symptoms to improve their health behavior by the researcher. Both groups were assessed at baseline, and results were followed up at the 4th, 8th, and 12th weeks, respectively.

Each subject was given his/her own logbook to record dates of practice, duration and frequency of

(a). Pelvic tilting



(b). Back extension

(c). Knee to chest

Fig 1. Back exercise positions.

exercises to better monitor exercise compliance. During the follow-up visits, the researcher asked each subject if they had received any concomitant treatment. If the answer was "YES", the type, dosage and intensity were recorded.

Statistical analysis

Data were analyzed using SPSS version 18.0.[23] Demographic and occupational information were presented as descriptive statistics. Data were reported quantitatively using mean ± SD and qualitatively as percentage and frequency. Two-way repeated measures ANOVA with Bonferroni correction was used to compare pain scores and the Thai version of the Oswestry questionnaire score. Intention-to-treat was used for missing data. A *P-value* < 0.05 was selected as statistically significant.

RESULTS

Demographic characteristics

Demographic data are presented in Table 1. Females strikingly outnumbered males in the specific nursing occupation; however, there was no significant difference between the study and control group. Mean age in the control group was higher than in the study group. Other characteristics such as body mass index (BMI), educational level, personal habits like smoking, alcohol consumption and level of activities were similar between the two groups. Two participants dropped out during the study period as a result of accidental injury and unwillingness to continue.

Occupational information

Occupational factors showed no difference between the training and control groups, except for the duration of working which was significantly longer for the control group than for the training group (*P-value = 0.024*) (Table 2). Likewise, mean age of the control group was higher than the training group, although it did not reach statistical significance (Table 1). One possibility for this could result from selection bias.

Pain score

The pain score showed interaction between both groups (*P-value < 0.001*). At each time point, significant differences were found between both groups. At the 4th week, the *P-value = 0.009*, 8th week *P-value = 0.001*, and 12th week *P-value < 0.001*. There were significant differences in the training group (*P-value < 0.001*) but no differences in the control group (*P-value = 0.658*) (Fig 2).

TABLE 1. Demographic characteristics of participants (Total n=58).

Characteristic	Total (n=58)	Training group (n_1=28)	Control group (n_2=30)	*P*-value
Sex				
Male	8	3 (10.7%)	5 (16.7%)	0.707
Female	50	25 (89.3%)	25 (83.3%)	
Age (years)		36.54 ± 8.89	41.67 ± 10.70	0.053
Body Mass Index (kg/m^2)		23.58 ± 4.29	23.56 ± 2.50	0.979
< 18.5 (Underweight)	4	3 (10.7%)	1 (3.3%)	0.414
18.5-22.9 (Normal range)	19	9 (32.1%)	10 (33.3%)	
23.0-24.9 (Overweight)	18	7 (25.0%)	11 (36.7%)	
25.0-29.9 (Obese class I)	15	7(25.0%)	8 (26.7%)	
≥ 30.0 (Obese class II)	2	2 (7.1%)	0 (0.0%)	
Education level				
Vocational certificate	19	10 (35.7%)	9 (30.0%)	0.445
Bachelor degree	29	15 (53.6%)	14 (46.7%)	
Higher than master degree	10	3 (10.7%)	7 (23.3%)	
Smoking habits				
Non-smoker	54	28 (100.0%)	26 (86.7%)	0.135
Ex-smoker	3	0 (0.0%)	3 (10.0%)	
Regular smoker	1	0 (0.0%)	1 (3.3%)	
Alcohol consumption				
Non-drinker	37	20 (71.4%)	17 (56.7%)	0.486
Ex-drinker	6	2 (7.1%)	4 (13.3%)	
Occasional drinker	15	6 (21.4%)	9 (30.0%)	
Leisure time physical activities				
Never	15	10 (35.7%)	5 (16.7%)	0.159
Sometimes	37	17 (60.7%)	20 (66.7%)	
Usually	3	0 (0.0%)	3 (10.0%)	
Always	3	1 (3.6%)	2 (6.7%)	
Congenital disease				
No	39	17 (60.7%)	22 (73.3%)	0.306
Yes	19	11 (39.3%)	8 (26.7%)	

TABLE 2. Occupational information of participants (Total n=58).

Characteristic	Total (n=58)	Training group (n_1=28)	Control group (n_2=30)	*P*-value
Nursing position				
Registered nurse	27	11 (39.3%)	16 (53.3%)	0.284
Practical nurse	31	17 (60.7%)	14 (46.7%)	
Ward				
Medical	23	12 (42.9%)	11 (36.7%)	0.630
Surgical	35	16 (57.1%)	19 (63.3%)	
Duration of working in ward (years)		13.66 ± 7.33	19.19 ± 10.42	0.024*
Overtime work				
Never	39	16 (57.1%)	23 (76.7%)	0.196
2-3 times per month	8	4 (14.3%)	4 (13.3%)	
2-3 times per week	8	5 (17.9%)	3 (10.0%)	
Almost everyday/Everyday	3	3 (10.7%)	0 (0.0%)	
Lifestyle outside the workplace				
Sitting >20 minutes				
No	18	11 (39.3%)	7 (23.3%)	0.189
Yes	40	17 (60.7%)	23 (76.7%)	
Standing >20 minutes				
No	14	6 (21.4%)	8 (26.7%)	0.641
Yes	44	22 (78.6%)	22 (73.3%)	
Walking >20 minutes				
No	6	2 (7.1%)	4 (13.3%)	0.671
Yes	52	26 (92.9%)	26 (86.7%)	
Use hand or arm repeatedly				
No	21	9 (32.1%)	12 (40.0%)	0.534
Yes	37	19 (67.9%)	18 (60.0%)	

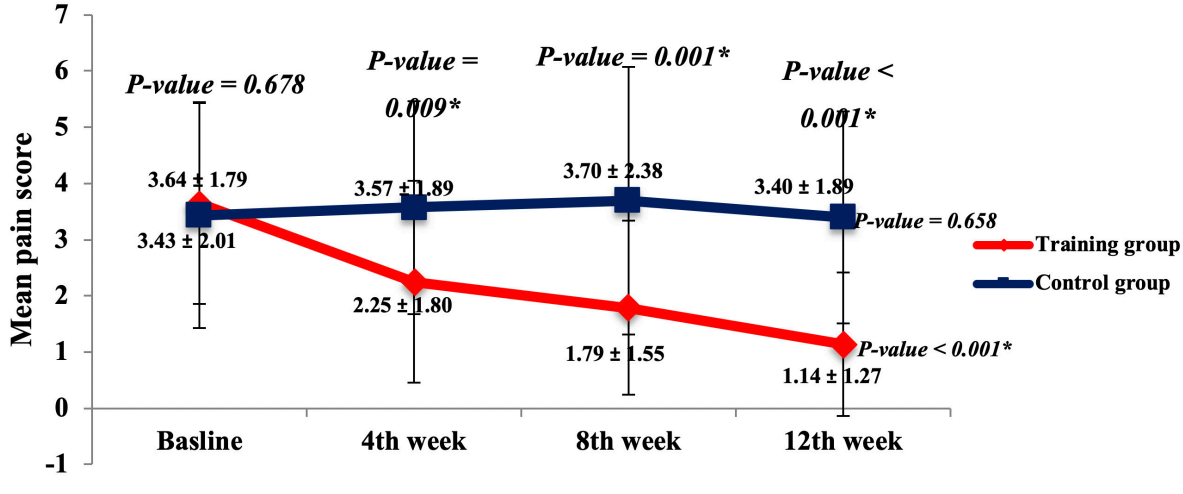


Fig 2. Comparison of pain score between training and control groups.

For the training group, LBP relief was significant at the 4th, 8th, and 12th weeks compared with pain at the baseline (*P-value < 0.001*). Pain score at the 12th week was significantly lower than at the 4th (*P-value < 0.001*) and 8th weeks (*P-value = 0.001*), while pain score at the 8th week was significantly lower than at the 4th week (*P-value = 0.004*). Pain scores remained the same in the control group at all time points.

Thai version of the Oswestry questionnaire score

Disabilities related to LBP using the Oswestry questionnaire score (Thai version) gave similar interactions between the training and control groups (*P-value < 0.001*). There were significant differences between both groups at the 8th week (*P-value = 0.001*) and 12th week (*P-value < 0.001*), while for each group, there were significant differences in the training group (*P-value < 0.001*) but no differences in the control group (*P-value = 0.323*) (Fig 3).

For the training group, disability scores at the 4th, 8th, and 12th weeks were significantly lower than the baseline (*P-value < 0.001*). The score at the 12th week was significantly lower than at the 4th (*P-value < 0.001*) and 8th weeks (*P-value = 0.026*), while the score at the 8th week was significantly lower than at the 4th week (*P-value = 0.001*) but no differences were observed in the control group at all time points.

Compliance with exercise was 85.7%. Four participants in the training group and five participants in the control group had concomitant treatment during the study; however, their scores were replaced with the last observation carried forward (LOCF) to maximize data reliability.

For statistical analysis, a two-way repeated measures ANOVA, including post hoc testing with Bonferroni correction, was used for comparisons between the training group and control group. Furthermore, intention-to-treat (ITT) was also used for data analysis. All participants, including those who withdrew, were included. However, participants who withdrew during the study had no data to analyze; if they followed the back exercise program, their pain score and Thai version of the Oswestry questionnaire score should be less than the baseline. Therefore, the last observation carried forward (LOCF) was used to replace the missing data. This technique ensured that the estimated result was similar to the actual data.[24]

DISCUSSION

The causes of lower back pain are complex and associated with abdominal and back muscle weakness, atrophy and loss of muscular endurance and flexibility. Back exercise forms part of the comprehensive treatment of LBP, emphasizing more active participation of patients particularly in chronic cases. Our results indicated that back exercise and education reduced pain and disability by following an exercise program for at least 3 days a week for 12 weeks. The back exercise program was designed for strength, endurance and flexibility training of the commonly involved muscles. Strengthening exercises were performed at least 2 days a week with at least 2-3 days a week for the flexibility exercises. Performing the exercise program for 12 weeks was necessary because no neuromuscular adaptation occurs within the first few weeks and exercise and muscle hypertrophy is typically experienced after 6 to 7 weeks of exercise.[25] Therefore,

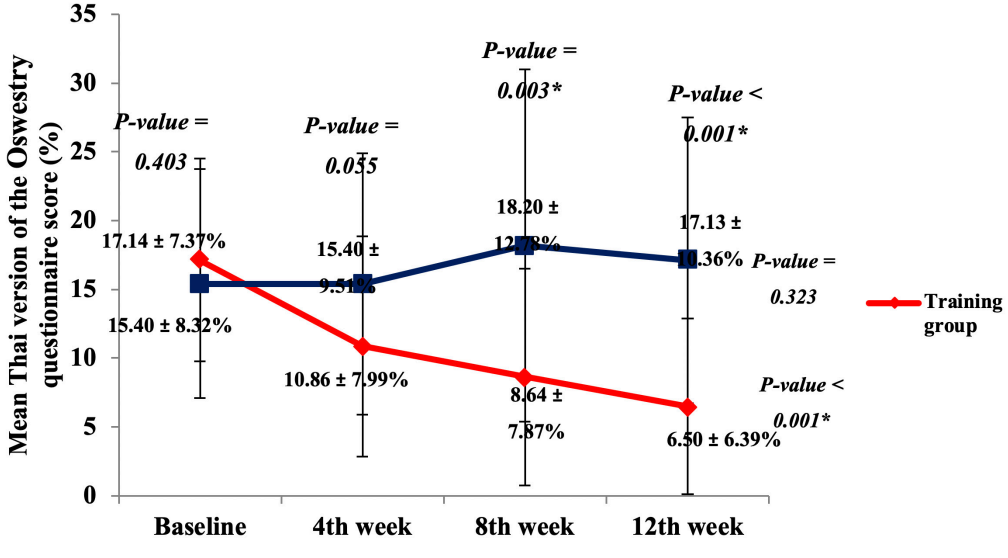


Fig 3. Comparison of the Thai version of the Oswestry questionnaire score between training and control groups.

a 12-week duration was selected as suitable for this study to prove the benefit of both biomechanical and physiological effects. Our results were consistent with other studies indicating that strengthening exercises reduced pain and disability associated with LBP after 6 weeks to 12 months of the exercise program.[26-31] Likewise, core muscle strengthening for at least 3 months was beneficial in aspects of pain relief and functional improvement. Nevertheless, no significant difference was demonstrated in exercise groups up to 12 months compared with the exercise group of over 12 months for participants with chronic LBP.[32] Furthermore, outcomes of core stability combined with general exercise were similar.[33]

In addition, our exercise program was combined with education to facilitate behavioral change, modify health beliefs and attitudes, and motivate the participants to follow the exercise program. Some studies suggested that education alone did not appear to prevent LBP but exercise combined with education showed a positive result.[16,34] Compliance with the exercise routine is a key success factor to combat chronic LBP. In this study, logbooks were given to participants for more accurate monitoring during the follow-up visits, with compliance of 85.7%.

Dealing with chronic LBP is a sophisticated process which involves not only pain relief but also functional restoration. CLBP is often heredity and not episodic like acute LBP; therefore, prevention is sometimes better than treatment. Strategies to prevent chronic pain involve early diagnosis and early treatment of acute pain conditions. At present, the concept of treatment is more aggressive for acute pain control. Some may argue that our study design was not consistent with the hypothesis. Unlike acute LBP, the study design for prevention is to reduce the recurrence of pain and prolong the duration of the new episode of pain which would be impossible and incompatible with the natural course. A prevention scheme in the context of chronic LBP in the workplace would involve limiting the progression of pain severity, disability and suffering. Here, we recruited CLBP subjects with mild to moderate pain severity that had minimal disability following the Thai version of the Oswestry questionnaire score. If CLBP progressed or more injuries took place, then pain and disability would be expected to flare up. However, both pain amelioration and functional improvement were shown at all time points compared with the control group. As mentioned above, our results supported the research hypothesis.

Demographic data and occupational information of participants showed no significant differences between the training and control groups except for duration of working. In the control group, duration of working was significantly longer than in the training group, possibly due to the mean age differences of the subjects as well as recruitment or setting bias. Mean age of the control group was higher than the training group although it did not reach statistical significance. Whether this difference affected pain severity and functional ability is doubtful. Degenerative change of the spine is more likely to develop in older people; however, it does not equate to back pain.

Back exercise programs combined with education are beneficial for nurses with CLBP who suffer from mild to moderate LBP with minimal disability. These may prevent clinical progression through pain reduction and functional improvement as an easy, low risk, self-managed way to control LBP.

There were some limitations in this study. Firstly, the follow-up period was rather short because of time limitations and maybe not long enough to demonstrate the flare-up of symptoms and recurrence. Secondly, participants were only subjectively measured by a questionnaire survey. Objective measurements were not conducted due to budget limitations.

CONCLUSION

Our results suggested that back exercise and education effectively relieved LBP and improved muscle function among nurses. Therefore, our proposed scheme for LBP prevention should be implemented in all tertiary hospitals in Thailand to improve both safety and working conditions of the nursing staff.

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Treatment Outcomes of Advanced Stage Endometrial Carcinoma (Stage III-IV) and Related Factors

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ABSTRACT

Objective: The aim of this study was to determine treatment response, the recurrence rate, 3-year overall survival, 3-year recurrence-free survival, and associated prognostic factors for survival among advanced-stage endometrial carcinoma patients at Siriraj Hospital.

Methods: This study was conducted at the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok, Thailand. A total of 415 patients that were diagnosed with advanced-stage endometrial carcinoma during January 1998 to December 2014 were enrolled. Data retrieved from medical records included baseline characteristics, surgico-pathological reports, treatment protocol, follow-up data, treatment response, and recurrence status. Three-year survival and recurrence-free survival were estimated by Kaplan-Meier method. Various factors were analyzed for significant association with survival.

Results: Four hundred of 415 cases were included in the final analysis. There were 282 (70.5%) and 118 (29.5%) patients that were diagnosed with stage III and IV disease, respectively. Two hundred and eighty-two patients had complete response after primary treatment, and 94 (33.3%) patients had disease recurrence. The median follow-up and survival times were 24.5 and 42.5 months, respectively. The 3-year survival rate was 50%, and the median recurrence-free interval was 12.25 months. Multivariate analysis revealed high-grade tumor histology, lymph node metastasis, Eastern Cooperative Oncology Group (ECOG) performance status, and menopausal status to be significant prognostic factors for overall survival.

Conclusion: Median survival among patients with advanced-stage endometrial carcinoma after primary treatment was 3 years. The significant prognostic factors were high grade tumor histology, lymph node metastasis, ECOG performance status, and menopausal status.

Keywords: Advanced stage; endometrial carcinoma; prognostic factor; recurrence; survival (Siriraj Med J 2020; 72: 117-124)

INTRODUCTION

Endometrial carcinoma is the most commonly occurring gynecologic cancer among women in Europe, America and others developed countries.[1] In Thailand, endometrial cancer is the third most common cancer of the female reproductive system after cervical cancer and ovarian cancer.[2] The incidence of endometrial cancer is increasing in Thailand.

Endometrial carcinoma have two different clinico-pathological subtypes. Type I, which is endometrioid or

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estrogen related, is more common than type II which is non-endometrioid or non-estrogen related.[1] Type I usually occurs in younger age or perimenopausal women with a history of exposure to unopposed estrogen and it is associated with endometrial hyperplasia or endometrial intraepithelial neoplasia (EIN). Type II occurs in women without estrogen stimulation, and may arise in a background of atrophic endometrium. Type II endometrial carcinoma tends to occur in older, thin, postmenopausal women and it is associated with a poorer prognosis.[1,3]

The stage of cancer depended on surgicopathological staging according to International Federation of Gynecology and Obstetrics (FIGO) staging system. Approximately 75-80% of women with endometrial carcinoma were diagnosed at early stage and had excellent treatment outcomes.[1] Conversely, advanced-stage patients (stage III-IV) who were diagnosed with extrauterine diseases had poor prognosis and worse treatment outcomes.[4]

Surgery is the primary treatment for endometrial carcinoma patients. Many studies in Europe and America investigated the use of adjuvant chemotherapy and/or radiation therapy to improve the survival of patients with advanced-stage diseases. The overall survival time among advanced-stage patients is about 12-15 months.[4-6] Alvaro, *et al*. reported histologic subtype, age, myometrial involvement, lympho-vascular space invasion, lymph node metastasis and residual tumor after surgery to be significantly associated with treatment outcomes in endometrial carcinoma.[7]

The objective of this study was to determine treatment response, the disease recurrence rate, 3-year overall survival, 3-year recurrence-free survival, and associated prognostic factors for survival among advanced-stage endometrial carcinoma patients at Siriraj Hospital – Thailand's largest national tertiary referral center regardless of modality of adjuvant treatment which was generally required in advanced-stage cancer. This was the database of Division of Gynecologic Oncology, Siriraj Hospital and use to be the data for counselling patients in this group.

MATERIALS AND METHODS

This retrospective study was conducted at the Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, Faculty of Medicine Siriraj Hospital. The protocol for this study was approved by Siriraj Institutional Review Board (Si 439/2017).

Endometrial cancer patients who were treated during January 1998 to December 2014, and who had surgically and/or clinically confirmed FIGO stage III-IV endometrial cancer based on FIGO 2009 system[8] were included. Patients who were treated before 2009 were restaged, and patients with previously diagnosed stage IIIA from positive cancer cells in peritoneal fluid alone were excluded from the study.

At our center, the standard operation included peritoneal washing for cytology and total hysterectomy with bilateral salpingo-oophorectomy. Among patients considered at-risk for extrauterine disease, such as high-grade tumor, large tumor volume, deep myometrial invasion or non-endometrioid subtype, pelvic and/or paraaortic lymphadenectomy or sampling was required. All of the preceding operative procedures were performed by gynecologic oncologists.

Response criteria was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Complete Response (CR) means disappearance of all known lesion(s). Partial Response (PR) means at least 30% decrease in the sum of diameters of known lesions, Progressive Disease (PD) means at least 20% increase in the sum of diameters of known lesions and/or the appearance of new lesion(s). Stable Disease (SD) means neither shrinkage nor increase to qualify for PR nor PD.[9] Patients that were previously evaluated for treatment response by World Health Organization (WHO) criteria or RECIST guideline version 1.0 were reevaluated using the current RECIST guideline version 1.1.

Follow-up data that was collected after complete treatment included careful history taking, and pelvic and physical examinations by gynecologic oncologist every 3 to 4 months for the first 2 years after treatment, every 6 months for the next 3 years and every year thereafter. Imaging study was performed when indicated. Recurrence of disease was defined as evidence of measurable disease and/or pathology/cytology confirmation.[9] The sites of recurrence were classified as local (intra-pelvic region), distant (extra-pelvic region) or both.

Sample size calculation

The sample size for this study was calculated based on the previously reported estimated 12 percent rate of advanced-stage among patients with endometrial carcinoma.[10] At least 451 patients were required to achieve 95% confidence level with a type I error at 0.05. Overall survival (OS) was defined as the time between the first date of primary treatment and the date of death from any cause or the last follow-up. Recurrence-free survival (RFS) was defined by the last date of primary treatment to the date of confirmed disease recurrence. This study did not separately analyzed the data of patients who had initially stable or progressive diseases, or the data of patients that received other alternative or second-

line treatments. These should, therefore, be considered possible confounding factors.

Statistical analysis

Descriptive statistics were used to assess and summarize patient baseline characteristics, surgical data, histopathology, treatment details, response status and recurrence status. Categorical data are shown as number and percentage, and continuous data are presented as mean plus/minus standard deviation. Duration of follow-up was defined as the date of last treatment to the date of death or last follow-up. OS and RFS were each estimated using the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard models were used to identify any statistically significant prognostic factors. Associations are reported as hazard ratios (HRs) and 95% confidence interval (CIs). *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics version 16 (SPSS, Inc., Chicago, IL, USA).

RESULTS

During January 1998 to December 2014, the incidence of endometrial cancer at our center was 1,456 cases, and 415 (28.5%) of those were diagnosed with advanced-stage (stage III/IV) endometrial carcinoma. Fifteen of 415 patients that had incomplete data and/or incorrect staging were excluded. The remaining 400 patients were included in our final analysis.

The mean age and body mass index (BMI) of patients in this study was 58.5 years and 25.4 kg/m^2, respectively. Three-quarters of cases were menopause at the time of diagnosis. Most patients presented with abnormal vaginal bleeding and had good performance status. Eighty-seven percent of cases (348/400) underwent primary surgery. Most (334/348) of those operations were performed via laparotomic approach. During surgery, 268 and 155 of 334 cases received pelvic and paraaortic nodal evaluation, respectively. Complete removal of disease was achieved in 270 of 348 cases that underwent primary surgery. The most common histologic subtype was endometrioid carcinoma (246/400, 61.5%). Fifty-four percent of cases had high-grade (grade 3) tumor histology. There were 282 (70.5%) and 118 (29.5%) cases that were diagnosed with stage III and IV disease at first diagnosis, respectively. Demographic, clinical, surgical and pathological characteristics of patients are shown in Table 1.

After complete primary treatment, complete response, partial response, stable disease and progression of disease was observed in 282 (70.5%), 7 (1.8%), 25 (6.2%) and 86 (21.5%) cases, respectively. Details relating to second-line or alternative treatment were not included in this study.

The median follow-up time was 24.5 months (interquartile range [IQR]: 3.3-53.1), and one-third (94/282) of complete response patients had disease recurrence. The median recurrence-free interval was 12.25 months (range: 0.99-80.49). The patterns of recurrence were intra-pelvis, extra-pelvis and both in 31.9% (30/94), 48.9% (46/94) and 19.2% (18/94) of patients, respectively. The 3-year recurrence-free survival (RFS) rate was 67%, the 3-year overall survival (OS) rate was 50%, and the median survival time was 42.5 months (range: 10.1-75.0). Fig 1 shows Kaplan-Meier survival analysis compared between stage III disease with stage IV disease.

Univariate analysis for factors significantly associated with OS and RFS is shown in Table 2. The factors significantly associated with OS included age, postmenopause status, performance status, residual tumor after primary surgery, non-endometrioid histologic subtype, tumor grading, FIGO staging, deep myometrial invasion, lymphovascular space invasion, positive peritoneal cytology, lymph node metastasis, extra-pelvic metastasis, receiving adjuvant treatment and initial treatment response. The factors significantly associated with RFS were age, postmenopause, non-endometrioid histologic subtype, tumor grading, FIGO stage IVB, deep myometrial invasion and extra-pelvic metastasis.

Multivariate analysis showed grade 3 tumor, lymph node metastasis, ECOG performance status and postmenopausal status to be significant prognostic factors for OS with adjusted hazard ratios (HRs) of 17.0 (95% confidence interval [CI]: 3.1-92.1), 8.5 (95% CI: 2.1-34.4), 7.8 (95% CI: 1.5-40.2), and 6.9 (95% CI: 2.3-20.2), respectively. Extra-pelvic metastasis, grade 3 tumor and age were significant factors for RFS with adjusted HRs of 10.4 (95% CI: 4.5-26.9), 9.5 (95% CI: 2.0-44.7), and 1.1 (95% CI: 1.0-1.1), respectively (Table 3).

DISCUSSION

The incidence rate of advanced stage (stage III, IV) endometrial carcinoma in this study was 28.5%, which is higher than the rates reported from previous studies. The incidence rate of advanced-stage endometrial carcinoma was 12% in a Taiwanese study, and 8.7% in a study by Alvaro, *et al.*[7,10] This difference in rates between our study and the aforementioned two studies can be explained by the fact that three-quarters of the patients in our study were menopause with a high proportion of high-grade tumor histology and non-endometrioid (non-estrogen-related) subtype, which has an aggressive

TABLE 1. Demographic and clinical characteristics of enrolled patients.

Characteristics	n (%)
Age (years), mean±SD	58.5±9.9
Presenting symptom, n (%)	
Abnormal vaginal bleeding	344 (86.0%)
Pelvic mass	17 (4.2%)
Pelvic pain	13 (3.2%)
Other	26 (6.5%)
Menopausal status	
Premenopause	101 (25.2%)
Postmenopause	299 (74.8%)
ECOG performance status, n (%)	
0	240 (60.0%)
1	122 (30.5%)
2	24 (6.0%)
3	14 (3.5%)
Primary surgery, n (%)	
No	52 (13.0%)
Yes	348 (87.0%)
Residual tumor, n (%)	
None	270 (67.5%)
≤1 cm	24 (6.0%)
>1 cm	54 (13.5%)
FIGO stage (2009), n (%)	
IIIA	94 (23.5%)
IIIB	34 (8.5%)
IIIC1	103 (25.8%)
IIIC2	51 (12.8%)
IVA	5 (1.2%)
IVB	113 (28.2%)
Histology, n (%)	
Endometrioid	246 (61.5%)
Non-endometrioid	154 (38.5%)
Tumor grade, n (%)	
Grade 1	65 (16.2%)
Grade 2	119 (29.8%)
Grade 3	216 (54.0%)
Peritoneal cytology, n (%)	
Negative for malignancy	214 (53.5%)
Positive for malignancy	73 (18.2%)
Lymph node metastasis, n (%)	
Negativity	94 (23.5%)
Only pelvic LN metastasis	116 (29.0%)
Only PAN metastasis	18 (4.5%)
Both pelvic LN and PAN metastases	45 (11.2%)
Adjuvant therapy, n (%)	
None	49 (12.2%)
CT alone	188 (47.0%)
RT alone	79 (19.8%)
Combined RT and CT	84 (21.0%)

Abbreviations: SD = standard deviation; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; pelvic LN = bilateral pelvic lymph node; PAN = paraaortic lymph node; CT = chemotherapy; RT = radiation therapy

TABLE 2. Univariate analysis for prognostic factors of overall survival and recurrence-free survival.

Factors	Overall survival		Recurrence-free survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.039 (1.022-1.057)	***<0.001***	1.041 (1.019-1.063)	***<0.001***
Menopausal status	2.595 (1.000-3.962)	***<0.001***	2.160 (1.290-3.618)	***0.003***
ECOG status				
ECOG 0	1		1	
ECOG 1	1.677 (1.169-2.404)	***0.005***	1.316 (0.846-2.048)	0.223
ECOG 2	5.312 (3.166-8.913)	***<0.001***	1.287 (0.403-4.111)	0.670
ECOG 3	9.948 (5.387-18.370)	***<0.001***	NA	NA
Residual tumor				
None	1		1	
≤1 cm	3.565 (2.076-6.121)	***<0.001***	2.371 (1.141-4.927)	***0.021***
>1 cm	3.819 (2.531-5.763)	***<0.001***	0.793 (0.344-1.824)	0.585
Histology				
Endometrioid	1		1	
Serous	3.542 (2.409-5.206)	***<0.001***	3.622 (2.191-5.986)	***<0.001***
Clear cell	2.629 (1.261-5.481)	***0.010***	1.535 (0.477-4.942)	0.472
Mucinous	9.356 (1.279-68.438)	***0.028***	NA	NA
Poorly-differentiated	6.902 (3.952-12.053)	***<0.001***	6.214 (2.427-15.908)	***<0.001***
Mixed	2.127 (1.261-3.587)	***0.005***	2.964 (1.623-5.413)	***<0.001***
Adenosquamous	1.557 (0.215-11.301)	0.662	NA	NA
Neuroendocrine	9.550 (2.307-39.535)	***0.002***	21.216 (2.822-159.502)	***0.003***
Carcinosarcoma	10.188 (4.046-25.650)	***<0.001***	19.279 (4.561-81.498)	***<0.001***
Tumor grading				
Grade 1	1		1	
Grade 2	2.038 (1.006-4.127)	***0.048***	2.636 (0.994-6.992)	0.051
Grade 3	6.112 (3.189-11.714)	***<0.001***	8.371 (3.365-20.824)	***<0.001***
FIGO staging				
Stage IIIA	1		1	
Stage IIIB	2.821 (1.377-5.777)	***0.005***	0.357 (0.084-1.513)	0.162
Stage IIIC1	1.803 (1.024-3.173)	***0.041***	1.156 (0.656-2.038)	0.616
Stage IIIC2	2.621 (1.427-4.816)	***0.002***	1.642 (0.872-3.094)	0.125
Stage IVA	16.762 (4.914-57.174)	***<0.001***	NA	NA
Stage IVB	6.527 (3.945-10.800)	***<0.001***	2.606 (1.500-4.525)	***0.001***
Myometrial invasion				
≤1/2	1		1	
>1/2	2.261 (1.502-3.405)	***<0.001***	1.712 (1.009-2.904)	***0.046***
LVSI	2.224 (1.391-3.555)	***0.001***	1.228 (0.755-1.997)	0.408
Peritoneal cytology positive for malignancy	1.806 (1.104-2.953)	***0.018***	1.504 (0.883-2.564)	0.133
Lymph node metastasis	3.834 (2.156-6.818)	***<0.001***	1.423 (0.867-2.335)	0.163
Pelvic LN positive alone	0.799 (0.421-1.518)	0.494	0.510 (0.232-1.120)	0.093
PAN positive alone	5.011 (1.678-14.963)	***0.004***	1.041 (0.294-3.693)	0.950
Both Pelvic and PAN	3.498 (1.964-6.227)	***<0.001***	1.955 (1.007-3.796)	***0.048***
Extrapelvic metastasis	3.863 (2.787-5.355)	***<0.001***	2.365 (1.516-3.688)	***<0.001***
Adjuvant treatment	0.345 (0.208-0.573)	***<0.001***	1.034 (0.419-2.549)	0.942
Treatment response				
Complete response	1			
Partial response	3.476 (1.263-9.564)	***0.016***		
Stable disease	9.410 (5.287-16.749)	***<0.001***		
Progressive disease	12.326 (8.443-17.994)	***<0.001***		

A p-value<0.05 indicates statistical significance

Abbreviations: HR = hazard ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; pelvic LN = bilateral pelvic lymph node; PAN = paraaortic lymph node

TABLE 3. Multivariate analysis for prognostic factors of overall survival and recurrence-free survival.

Factors	Overall survival		Recurrence-free survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	0.962 (0.908-1.020)	0.195	1.061 (1.008-1.117)	***0.024***
Menopausal status	6.874 (2.343-20.168)	***<0.001***	1.049 (0.301-3.652)	0.940
ECOG status				
ECOG 0	1			
ECOG 1	0.405 (0.165-0.998)	0.050		
ECOG 2	7.845 (1.533-40.129)	***0.013***		
ECOG 3	NA	NA		
Residual tumor				
None	1		1	
≤1 cm	4.054 (0.786-20.909)	0.094	1.968 (0.365-10.596)	0.431
>1 cm	2.573 (0.823-8.049)	0.104	0.467 (0.054-4.045)	0.489
Histology				
Endometrioid	1		1	
Serous	0.711 (0.277-1.829)	0.480	0.950 (0335-2.693)	0.923
Clear cell	1.883 (0.436-8.134)	0.396	0.597 (0.071-5.032)	0.597
Mucinous	NA	NA	0.507 (0.005-53.745)	0.775
Poorly-differentiated	NA	NA	5.010 (1.196-20.993)	***0.028***
Mixed	2.154 (0.685-6.773)	0.189	1.318 (0.464-3.743)	0.604
Adenosquamous	NA	NA	1.040 (0.018-58.781)	0.985
Neuroendocrine	2.904 (0.316-26.662)	0.346	7.477 (0.731-76.501)	0.090
Carcinosarcoma	0.051 (0.005-0.556)	***0.015***	0.697 (0.060-8.077)	0.773
Tumor grading				
Grade 1	1		1	
Grade 2	2.765 (0.495-15.453)	0.247	2.492 (0.507-12.250)	0.261
Grade 3	17.018 (3.143-92.135)	***0.001***	9.526 (2.029-44.727)	***0.004***
FIGO staging				
Stage III	1		1	
Stage IV	4.866 (0.001-7.439)	0.884	0.415 (0.001-2.127)	0.840
Myometrial invasion				
≤1/2	1		1	
>1/2	0.950 (0.372-2.429)	0.915	1.273 (0.583-2.782)	0.545
LVSI	1.467 (0.658-3.272)	0.349		
Peritoneal cytology positive for malignancy	0.957 (0.375-2.443)	0.927		
Lymph node metastasis	8.496 (2.100-34.363)	***0.003***		
PAN positive alone	4.561 (1.665-12.499)	***0.003***		
Both pelvic and PAN	4.337 (1.838-10.233)	***0.001***	1.273 (0.536-3.024)	0.584
Extrapelvic metastasis	0.001 (0.000-3.942)	0.912	10.379 (4.534-26.873)	***0.004***

A p-value<0.05 indicates statistical significance

Abbreviations: HR = hazard ratio; CI = confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; pelvic LN = bilateral pelvic lymph node; PAN, paraaortic lymph node

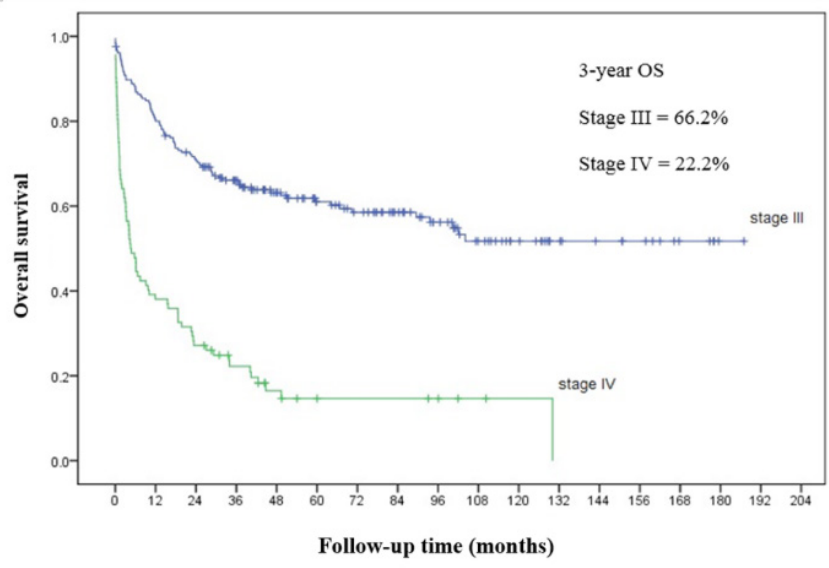

Fig 1. Kaplan-Meier subgroup analysis of overall survival according to FIGO staging in advanced stage endometrial carcinoma patients.

nature. The combination of these factors increased the number of patients with advanced-stage disease.

The age group that had the most advanced-stage endometrial cancer from Surveillance, Epidemiology and End Results (SEER) data was 55-64 years, and this is similar to the mean age at first diagnosis of 58.5 years in our study[11]. Abnormal vaginal bleeding was the most common presentation. Although they were diagnosed with advanced stage, most of the patients in our study had good performance status (ECOG 0-1) at diagnosis, so we could not predict the severity of disease by patient performance or clinical symptoms. The most common histologic subtype was endometrioid subtype, but the proportions of non-endometrioid subtype and high-grade tumor differentiation were both higher when compared to the proportions previously reported for all stages of endometrial carcinoma.[7] These differences in findings may be attributable to difference among races, as suggested by Koshiyama, *et al*. That group found different histologic subtypes of epithelial ovarian cancer among different nationalities.[12]

The 3-year OS of advanced-stage endometrial cancer in this study was 50%. This is similar to the 48.8% rate reported by Alvaro, *et al.*[7], but it is lower than the rate reported from a Taiwanese study that included only endometrioid subtype.[10] Our result showed that patient survival decreased rapidly when they did not achieve complete response after primary treatment. Approximately seventy percent of had evidence of extra-pelvic recurrence, which is consistent with hematogenous spreading in advanced-stage cancer. Systemic adjuvant therapy should, therefore, be considered in advanced-stage endometrial carcinoma even though the survival benefit of adjuvant treatment is inconclusive and still being debated.[13,14]

Univariate analysis showed multiple factors affected OS and RFS in advanced-stage endometrial carcinoma. Subsequent multivariate analysis revealed the most significant prognostic factors for OS to be grade 3 tumor (similar to previous studies[14-16]), lymph node metastasis, ECOG performance status and postmenopausal status. Extra-pelvic metastasis, tumor grading and age were significant prognostic factors for RFS.

Limitations

This study has some mentionable limitations. First, the total number of enrolled cases in this study was smaller than the calculated sample size, which means that our study may have lacked the statistical power needed to identify all significant associations and differences. However, the incidence rate of advanced-stage endometrial cancer in this study was higher than the rates reported from previous studies.[7,10] Moreover, our sample size was larger than the sample size from any other single-center study reported from Thailand. However, this can be improved the accuracy and reliability of the results by multicenter study. Secondly, this study did not separately analyzed data from patients who had initially stable or progressive diseases, or from patients received other alternative or second-line treatment, and both of these factors could affect patient survival. Lastly, the retrospective, non-randomized nature of data collection resulted in some incomplete information.

In conclusion, the results of this study revealed a rate of advanced-stage endometrial cancer at first diagnosis of 28.5%. Seventy percent of patients had complete response after primary treatment. The 3-year recurrence free survival (RFS) rate was 67%, and about half of patients succumbed to their disease within 3 years after primary

treatment. The significant prognostic factors for overall survival were grade 3 tumor, lymph node metastasis, ECOG performance status and postmenopausal status.

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Pediatric Neuromuscular Diseases Prevalence in Siriraj Hospital, Thailand's Largest Tertiary Referral Hospital

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ABSTRACT

Objective: There are no epidemiological data on childhood neuromuscular diseases in Thailand. We aimed to estimate the proportion of NMDs among pediatric neurology patients in Siriraj Hospital and determine the specific diagnosis.

Methods: A retrospective study was conducted in the pediatric neuromuscular clinic at Siriraj Hospital between 2014 and 2016.

Results: Of 1,994 patients aged < 21 years with neurological diseases, 217 (10.88 %) had received a diagnosis. Diagnostic clarity can be achieved using clinical tools such as electromyography, serum creatinine kinase, muscle histo-immunology, and genetic analysis. Of the 217 patients, 143 (65.9 %) had inherited and 74 (34.1%) had acquired neuromuscular diseases. The most common inherited NMD were the Dystrophinopathies, including Duchenne / Becker muscular dystrophy (n = 58), while spinal muscular atrophy was the second most common (n = 25). Myasthenia Gravis was the most common acquired neuromuscular disease (n = 36).

Conclusion: We found 10.88 percent of patients with neurological diseases have NMD. NMD is a chronic disease with poor quality of life and so multidisciplinary clinical care is crucial for these patients. In order to improve the standard of care, collaboration with government and other tertiary hospitals is important and will help serve a growing population of NMD patients.

Keywords: Neuromuscular diseases; neurology; Duchenne Muscular Dystrophy; spinal muscular atrophy (Siriraj Med J 2020; 72: 125-131)

INTRODUCTION

Neuromuscular diseases (NMD) usually result in chronic long-term disabilities and pose a significant burden to society and the healthcare system. Most NMD patients will need multi-disciplinary care due to complications in multiple organ systems including joint contractures, respiratory failure and cardiomyopathy. NMD can be either inherited or acquired. It is important to precisely diagnose patients since most acquired NMD can be effectively treated. For inherited NMD, genetic counseling is crucial to prevent inheritance (transmission) to the next generation.

Neuromuscular disorders (NMD) can be broadly divided by the location of the pathological lesions into those affecting anterior horn cell (AHC), peripheral nerve, neuromuscular junction (NMJ) and muscle fibers.[1-3] Epidemiologic research that explores NMD types, frequency and their associated genotypic distribution among the

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population is important to prioritize healthcare resource allocation. Emery[2] conducted a comprehensive literature review and estimated the global prevalence of inherited neuromuscular diseases to be $28.6x10^{-5}$ or 1 in 3,500. Other studies have reported a higher prevalence. For example, in Northern Ireland the prevalence of inherited NMD in patients age 0-84 years was estimated to be $34.5x10^{-5}$ or 1 in 2,900.[4] A study of childhood neuromuscular diseases (age 0-15 years) in western Sweden[5] reported the prevalence to be $63.1x10^{-5}$ for all neuromuscular diseases and $53.1x10^{-5}$ for inherited neuromuscular diseases. This study also reported that in 227 children with NMDs, 191 (84%) had inherited NMDs. In contrast, a study of Chinese children with NMDs (age <19 years old) in Hong Kong[6] reported a prevalence of $21.4x10^{-5}$ or 1 in 4,669. In the Chinese study, the investigators found that (68%) of 332 children with NMD had inherited disease. For prevalence of inherited muscle diseases, a study from Northern England reports $37.0x10^{-5}$ According to these studies, the most common inherited NMD are muscular diseases, followed by anterior horn cell and peripheral nerve diseases.[4-8]

Few studies have examined the prevalence and proportion of inherited NMD in childhood and none were conducted in Thailand. Worldwide, the diagnosis of inherited NMD is improving, especially for those involving single genes. For the more complex diseases involving multiple genes, the diagnosis still largely depends on the technical capability of each institution. This, in turn, affects healthcare resource allocation. There is currently no cure for inheritable NMD. Therefore, genetic counseling is essential to achieve a disease-free state in at-risk individuals and their offspring who are disease carriers.

The Multidisciplinary Neuromuscular Clinic at Siriraj Hospital is the largest tertiary care referral center in Thailand. Each year, the clinic sees (diagnoses?) over 100 (new?) cases of pediatric NMD. An understanding of the proportion of inherited NMD can provide insight into the urgent need for genetic diagnosis, counseling and intervention in this vulnerable patient population. Epidemiologic research is important in all ethnic groups to gain understanding about genetic parameters, inform healthcare planning, and to enable interethnic group comparisons. This study will also contribute to the development of a registry that will prepare our hospital for future clinical trials of new therapeutic agents. The data will also support resource management decisions, policy planning, and the allocation of rehabilitation and social welfare program funds.[5,6,9,10] It is difficult to estimate the prevalence of neuromuscular diseases in Thailand since there are multiple academic hospitals treating these patients. Siriraj Hospital is Thailand's largest tertiary hospital with more than 2,000 beds. The distinct different from other hospital is that Siriraj has pediatric neuromuscular clinic which is considered the first one in Thailand. Our data represents the proportion of NMDs among other pediatric neurological diseases in Siriraj Hospital. Therefore, we conducted a retrospectivestudy of the clinical characteristics of NMD children that receive care at the neuromuscular clinic (NMC) at Siriraj Hospital, the largest academic medical center in Thailand.

MATERIALS AND METHODS

Objective

To report the number and specific diagnosis of NMD cases referred to Neuromuscular Clinic at Siriraj Hospital in Bangkok, Thailand, with a focus on the proportion of inherited NMDs found in this population.

Methods

This was a retrospective study of patients aged 0-21 years with pediatric neuromuscular disease and pediatric neurologic disease at Siriraj Hospital between July 2014 and December 2016. The institutional Review Board at Faculty of Medicine Siriraj Hospital Mahidol University approved the study (Si 724/2015). Patients were seen in the neurology clinic or neuromuscular clinic. The Neuromuscular clinic is a multi-disciplinary clinic that offers specialist care in Pediatric Neurology, Rehabilitation, Orthosis, Physical Therapy and social work. We used Emery's criteria and the classification of the World Federation of Neurology Research Committee Group on Neuromuscular Disease[2,11,12] to make the diagnosis. A pediatric neurologist specializing in neuromuscular disease examined all patients. Appropriate investigations including nerve conduct study (NCS), serum creatinine kinase (CK), electromyography (EMG), muscle biopsy and molecular genetic study were performed to establish the diagnosis. Approximately 90% of all patient received full investigations, the rest are diagnosed by clinical diagnosis for partial investigation. Demographic data, socioeconomic status, clinical manifestations, complications and treatment of the disease were collected.

Operational definitions: neuromuscular disorders affect the nerves that control motor or sensory functions and the muscle itself, other neurological disorders in this manuscript means that the neurological disorders that are not neuromuscular disorders, and inherited NMDs are neuromuscular disorders that cause by a broad group of genetic conditions.

RESULTS

There were 217 children with NMD who followed up at the Pediatric Neurology Clinic, representing 10.88% of all patients with neurologic disease who presented to the clinic during the study period. One hundred forty-three patients (65.9%) had inherited neuromuscular diseases. (Table 1). The most common inherited NMD is Dystrophinopathies (Duchenne Muscular Dystrophy (DMD)/Becker Muscular Dystrophy (BMD)) (n=58). (Table 2) The second most common is Spinal Muscular Atrophy (SMA) (n= 25), followed by Hereditary Motor Sensory Neuropathy (HMSN) (n= 16). The most common acquired NMD was Myasthenia Gravis (MG) (n=36), followed by Brachial Plexus Injury (n=9), and Acute Inflammatory Demyelinating Polyneuropathy (AIDP) (n=7), respectively. (Table 3) Thirty-five of these 143 patients (24%) also had a positive family history of a similar disorder in a first or second-degree relative. (Table 4)

Since the Dystrophinopathies are the most common inherited neuromuscular disease found in our NMC clinic, we also collected further clinical information from these patients (Table 5). Twenty-six (45%) DMD patients were ambulatory. Of the 58 DMD patients, 55 were sent for genetic study (54 sent for Multiplex Ligation-dependent Probe Amplification (MLPA) and 1 sent for Polymerase chain reaction (PCR). Twenty-nine (50%) were diagnosed by MLPA, while the test showed no abnormality in the remaining 26 patients. Seven DMD patients were not receiving steroids due to side effects including obesity. SMA was the second most common inherited neuromuscular disease (Table 6). All SMA patients received genetic study (PCR or Denaturing High Performance Liquid Chromatography (DHPLC)), however one patient result was missing because he was diagnosed at a different hospital. Overall, 76% of the patients had exon 7&8 deletion of the SMN1 gene. 60% of these patients were SMA type II.

DISCUSSION

The estimated prevalence of neuromuscular disease among patients with neurological diseases was 10%, similar to a previous report.[13] The majority of neuromuscular diseases in our pediatric patients are inherited in nature. Even with muscle biopsy however, it is sometimes difficult to conclude if the etiology is acquired or inherited. In these cases, next generation sequencing is a promising tool for patient care. Interestingly, with the arrival of detailed genetic testing and sophisticated histo-immunochemical staining methods, established diagnoses are sometimes changed.

We found that inherited NMDs constituted 65.9% of all NMDs, similar to a report from Hong Kong. That study also found that Dystrophinopathies followed by SMA, were the most common NMD.[6] A Swedish study,[5] reported a higher percentage of inherited NMDs (84%) and the most common diseases were Hereditary Motor Sensory Neuropathy (HMSN), Dystrophinopathies and SMA, respectively. However, when the dataset includes adult patients such as in studies from Northern Ireland[4] and Northern England,[8] the most common neuromuscular disease becomes Myotonic Dystrophy then followed by DMD. This may be due to pediatric patients with Myotonic Dystrophy normally having mild disease severity compare to other congenital neuromuscular diseases, so they don't seek medical attention. Since the most common inherited neuromuscular diseases in children are not different from previous studies, we can conclude that ethnicity is not an important etiological factor. The previous studies done in all age group show differently because the age different of population. Four patients were diagnosed with Nonspecific muscle disease, due to limited diagnostic resources, especially advance immunochemistry and next generation sequencing. A collaboration with an international neuro-genetic center would be helpful for these patients.

TABLE 1. A 217 patients with neuromuscular diseases classify by neuroanatomy and etiology.

Location	Inherited	Acquired
Anterior horn cell	25 (11.52%)	2 (0.92%)
Peripheral nerve	16 (7.37%)	28 (12.90%)
Neuromuscular junction	3 (1.38%)	36 (16.59%)
Muscle	99 (45.62%)	8 (3.69%)
Total	143 (65.9%)	74 (34.1%)

TABLE 2. Detail of specific neuromuscular diseases including acquired and inherited, categorize by anatomical origin.

	N
Anterior Horn Cell (AHC)	
Spinal Muscular Atrophy (SMA)	25
Monomelic Amyotrophy (MMA)	2
Peripheral Nerve (PNS)	
Hereditary Motor Sensory Neuropathy (HMSN)	16
Brachial Plexus Injury	9
Peroneal Nerve Injury	4
Sciatic Neuropathy	2
Left L2-4 Plexopathy	1
Acute Inflammatory Demyelinating Polyneuropathy (AIDP)	7
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	3
Diabetic Polyneuropathy	1
Acute Motor Axonal Neuropathy (AMAN)	1
Neuromuscular Junction (NMJ)	
Congenital Myasthenic Syndrome (CMS)	3
Myasthenia Gravis	36
Muscle	
Muscular Dystrophy*	79
Congenital Myopathy*	10
HyperCKemia	1
Mitochondria/Metabolic Myopathy*	5
Polymyositis	4
Juvenile Dermatomyositis	2
Necrotizing Autoimmune myositis	2
Nonspecific muscle disease	4

*Please find more diagnosis detail for inherited muscular dystrophy, congenital myopathy and mitochondria/metabolic myopathy in Table 3.

TABLE 3. Detail of 99 patient with inherited muscular dystrophy, congenital myopathy and mitochondria/metabolic myopathy.

	N
Muscular Dystrophy	
Duchenne Muscular Dystrophy (DMD) /Becker Muscular Dystrophy (BMD)	58
Congenital Muscular Dystrophy (CMD)	6
Emery-Dreifuss Muscular Dystrophy (EDMD)	3
Ullrich Congenital Muscular Dystrophy (UCMD)	2
COL6A1 Congenital Muscular Dystrophy	2
Facioscapulohumeral muscular dystrophy (FSHD)	2
Limb-girdle muscular dystrophy (LGMD) type IIB	1
Non-specific Muscular Dystrophy	5
Congenital Myopathy	
Congenital Myopathy (Non-specific)	7
Congenital Myopathy Uniform type 1	1
Myofibrillar Myopathy	1
Congenital Myopathy (Titin)	
Mitochondria/Metabolic Myopathy	1
Glutaric aciduria type II with myopathy	3
Hypokalemia Periodic Paralysis (PP)	2
Nonspecific muscle disease	4

TABLE 4. The detail of 35 inherited neuromuscular disorders cases with positive family history.

Inherited neuromuscular disorders	Positive Family History Cases	Affected Family
DMD	16/58 (28%)	11/53 (21%)
CMT	4/16 (25%)	4/16 (25%)
SMA	1/25 (4%)	1/25 (4%)
Other	14/44 (32%)	9/39 (23%)
Total	**35/143 (24%)**	**25/133 (19%)**

TABLE 5. The characteristic of 58 DMD patients.

	Value
Clinical Stage	
Early ambulatory	17 (29.3%)*
Late ambulatory	9 (15.5%)*
Early non-ambulatory	19 (32.8%)*
Late non-ambulatory	13 (22.4%)*
CPK level (n=50)	22,182 ± 56,008 (3,517 - 405,418)**
Diagnosis by MLPA	29 (50%)*
Deletion	24 (41.1%)*
Duplication	5 (8.6%)*
Restrictive Lung	10 (17.2%)
Cardiomyopathy	8 (13.8%)
Steroid	51 (87.9%)

*n (%), **mean ± SD

TABLE 6. The characteristic of SMA patients (n=25).

	Value
Type	
Type I (0-6 mo.) Non-Sitter	2 (8%)*
Type II (7-18 mo.) Sitter	15 (60%)*
Type IIIA (>18 mo.) Walker and age onset < 3 years	4 (16%)*
Type IIIB (>18 mo.) Walker and age onset > 3 years	4 (16%)*
Exon 7&8 deletion	19 (76%)*
Exon 7 deletion	5 (20%)*

*n (%)

The second most common inherited NMD in our study was SMA, a disease that is often reported to be associated with SNM1 gene deletion in exon 7. In a separate study, we found deletions in both exon 7 and 8.[14] We also reported that SMA type II was the most common in our patient population, while another study reported Type I as most common.[15] This reflects our status as a provider of tertiary care neurologic consultation. Those with SMA type I whose disease is severe may not have been referred in time to receive our care. This difference could also be due to the fact that the diagnosis of SMA type I is typically made early in the course of disease by a geneticist, and these patients may die before being evaluated by neurologist or geneticist.

Despite representing only 10% of all patients, management of the pediatric neuromuscular disease population is challenging. These diseases are chronic, progressive and are associated with severe disability from joint contractures, respiratory failure, cardiomyopathy and scoliosis, while most patients have intact cognition. The goal of supportive care is to prevent complications and provide physical therapy to overcome limitations and improve quality of life. Hence, multidisciplinary management in an established neuromuscular clinic is crucial to improve quality of life for these patients. Prenatal diagnosis also plays important role since inherited NMDs often affect family members in different generations. Therefore, intervention to prevent the disease in offspring can decrease disease prevalence[3] as well as reduce social and healthcare costs. The limitation of the study also include that this study is single center study, thus we can't provide the information about the prevalence of neuromuscular disease in Thailand.

CONCLUSION

We found 10.88 percent of patients with neurological diseases have NMD. The majority of children with NMD who follow up at Siriraj Hospital had Duchenne Muscular Dystrophy, Hereditary Motor Sensory Neuropathy and Spinal Muscular Atrophy. Childhood NMD is a chronic disease with poor quality of life and so multidisciplinary clinical care is crucial for these patients. In order to improve the standard of care, collaboration with government and other tertiary hospitals is important and will help serve a growing population of NMD patients. Limited access to advanced diagnostic modalities prevents proper diagnosis in some patients. A future collaboration with an international genetics research center would be an important step forward to help establish a disease registry and improve genetic counseling in Thailand. National treatment guidelines and uniform implementation in pediatric neuromuscular disease clinics is needed for Thailand and other developing countries.

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Long-Term Outcomes of Group-Based Treatment for Obese Children and Adolescents

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ABSTRACT

Objective: A 1-year, group-based, treatment program with parental involvement was conducted on 115 obese youths during 2006-2011. The intervention decreased obesity severity. The current study assessed the participants' long-term weight loss and obesity-related complications.

Methods: Participants were invited for a single visit. Their weights, heights, and waist circumferences were measured and compared with corresponding figures at group-based treatment program completion. Factors associated with changed percentage weight-for-height (%W/H) were assessed.

Results: There were 43 subjects, including 6 participating telephonically. The median follow-up duration was 5.8 years. %W/H, BMI, and waist circumference increased significantly (p = 0.012, 0.002, and 0.003, respectively). %W/H rose for 26 participants (60.5%; failed group) but declined or stabilized for 17 (39.5%; successful group). The successful-group exercise duration and frequency were significantly higher (p = 0.006 and 0.018, respectively). Three participants had type 2 diabetes, including 1 known case, all in the failed group. Newly-found obesity-related disorders were elevated transaminases (6 participants, with 5 from the failed group), elevated blood pressure (1 failed-group participant), and dyslipidemia (one from each group).

Conclusion: Only 40% of the participants maintained long-term weight reduction. Regular exercise was associated with successful weight maintenance. Obesity-related complications were common in the failed group.

Keywords: Obese; child; adolescent; group-based treatment; outcome (Siriraj Med J 2020; 72: 132-139)

INTRODUCTION

Obesity among children and adolescents is increasing globally, leading to numerous health problems.[1,2] Complications such as type 2 diabetes (T2DM), metabolic syndrome, hypertension, and dyslipidemia are as common among obese children as among obese adults.[1,2] Adolescent obesity is associated with increased adulthood mortality from ischemic heart disease, metabolic diseases, respiratory diseases, etc.[3] It is therefore imperative to address obesity early to obviate detrimental health effects in adulthood.

Childhood obesity treatment involves dietary control, increased physical activity, and lifestyle changes. Phamarcotherapy should only be considered for adolescents unable to reduce weight via intensive lifestyle modifications, and bariatric surgery is only recommended for severely obese adolescents of final or near-final height with extreme complications.[4] The treatment goals are weight maintenance or gradual weight loss, depending on age and obesity degree.[5]

At our institute, a 1-year, group-based treatment program with parental involvement was conducted during 2006-2011.[6] Participants underwent behavioral modification as inpatients at the start of the program and via 5, group-based, outpatient sessions in months 1, 2,

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3, 6, and 9. The detail of the intervention was previously described.[6] Of the 126 participants (mean age 12.3 years), 115 completed the program. By program-end, the percentage weight-for-height (%W/H) and percentage body fat had decreased significantly (181.8 ± 39.1% vs. 169.3 ± 36.3%, $p < 0.001$; and 48.2 ± 5.1% vs. 45.0 ± 6.8%, $p < 0.001$, respectively). Moreover, glucose metabolism, lipid profiles, and liver functions had improved.[6]

Although our program produced successful weight management at the end of the 1-year intervention, long-term weight-maintenance data was lacking. Previous studies[7-9] that demonstrated long-term successful weight loss, had more intensive intervention with more frequent sessions than our program. This study aimed to examine the long-term impact of our 1-year, group-based treatment program, consisting of an initial hospitalization and 5 outpatient sessions, on weight maintenance and obesity-related complications, and factors associated with weight-control success.

MATERIALS AND METHODS

A cross-sectional study of the participants of the 1-year, group-based program was conducted at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, during 2014-2016. Participants were invited by telephone or mail to a single visit to obtain anthropometric measurements; if unable to attend, a phone interview was conducted. The number of daily meals, frequency and duration of exercise (all intensity of aerobic exercise, anaerobic exercise and any physical activity were included), interim obesity treatment (including follow-up at our Pediatric Endocrine clinic and/or at other Hospital), and healthy lifestyle habits (healthy eating and regular exercise) were collected. Participants with %W/H > 120% were defined as obese[10] and were advised to test for fasting blood sugar (FBS), lipid profile, and liver enzymes.

Blood tests were performed after overnight fasting. Glucose was measured using an automated analyzer (Integra 800/Cobas 8000; Roche Diagnostics, Manheim, Germany). Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, ALT, and AST were measured using a biochemical autoanalyzer (Cobas 8000; Roche Diagnostics). HbA1c was determined using turbidimetric inhibition immunoassay (Integra 800 CTS, Roche Diagnostics).

Participants whose %W/H had risen since program-end were categorized as "failed"; those with reduced or maintained %W/H were deemed "successful".

Siriraj Ethics Committee, Mahidol University, approved this study. All participants gave informed consent (Si 626/2013).

Statistical analysis

To make comparisons between the participants and the unreachable/non-participating individuals, and between the failed and successful weight-control groups, independent t-tests were used for the normally distributed data, and Mann–Whitney U tests for the non-normally distributed data. Comparisons of the clinical and biochemical data at program-end and long-term follow-up were performed by paired t-test for the normally distributed data and Wilcoxon signed-rank test for the non-normally distributed data. Logistic regression analysis identified the weight-management strategies associated with successful weight maintenance after program-end: 1) no treatment nor continued healthy lifestyle; 2) continued follow-up at our clinic; and 3) continued healthy lifestyle (diet control and regular exercise) for at least 12 months preceding this study. A chi-square test was performed to assess the difference in the numbers of participants for each treatment strategy in the failed and successful groups. The normally distributed data were presented as mean ± standard deviation, and the non-normally distributed data as median (min, max). Statistical significance was $p < 0.05$. Data were analyzed using SPSS (version 18.0).

RESULTS

Out of 115 participants who completed the 1-year group-based program, 37 participants enrolled, and another 6 were interviewed telephonically (22 males and 21 females). Fourteen declined, and 58 were unreachable (Fig 1).

Demographic data at the end of the group-based obesity treatment program of the participants and non-participants were similar, except the non-participants had longer durations after completing their weight-treatment programs (Table 1).

Overall, obesity severity had worsened since program-end (Table 2). Twenty-six participants (60.5%), consisting of 14 males and 12 females, had increased %W/H (failed group); the remaining 17 participants (39.5%), consisting of 8 males and 9 females, had a maintained or decreased %W/H (successful group). The successful group exercised more frequently than the failed group (4.7 ± 2.0 vs. 2.9 ± 2.7 days/week, $p = 0.018$), and for longer (240 [80,1890] vs. 110 [0,900] min/week, $p = 0.006$; Table 3).

As to treatment following program-end, 25 participants (58.1%) did not continue healthy lifestyles nor receive weight-reduction treatment during the preceding year. Twenty of those (80%) were in the failed group. Of the 14 participants (32.6%) continuing healthy lifestyles

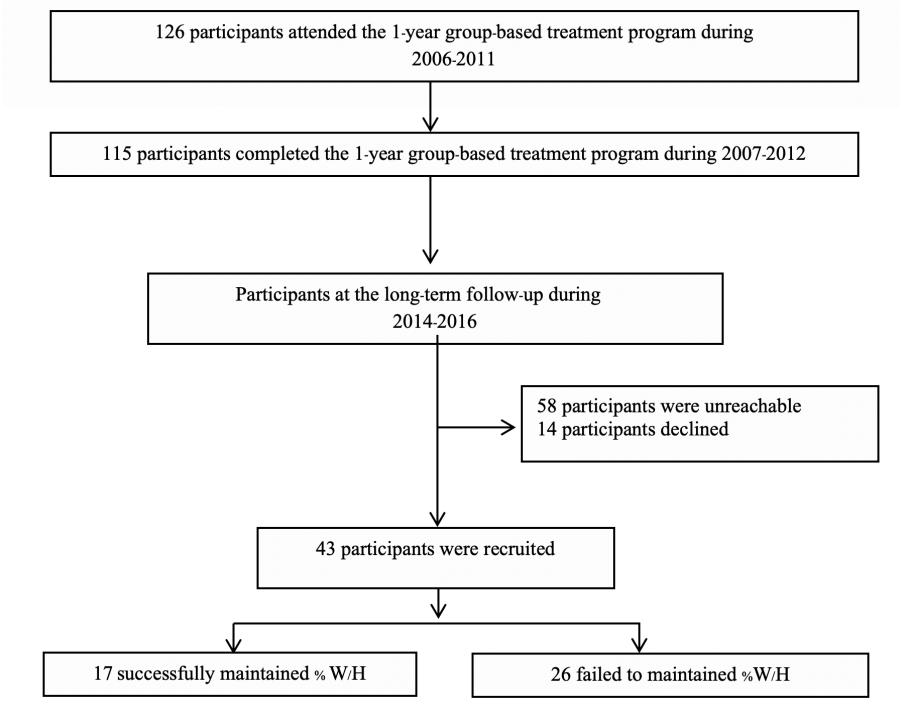

Fig 1. Numbers of participants at the beginning of the 1-year intervention, at the end of the intervention, and at the long-term follow-up.

TABLE 1. Comparison of demographic characteristics at the end of the group-based program of participating and unreachable/non-participating volunteers.

Data	Participating volunteers (n = 43)	Unreachable/ non-participating group (n = 72)	*P*-value
Male[a], person	22 (51.2)	37 (51.4)	0.981
Age (years)	13.2 ± 2.2	13.4 ± 2.0	0.548
%W/H (%)	167.2 ± 32.8	170.1 ± 37.6	0.670
BMI (kg/m^2)	31.9 ± 6.5	32.6 ± 7.1	0.570
Waist (cm)	94.0 ± 14.1	95.6 ± 13.8	0.548
Waist-height ratio	0.59 ± 0.1	0.59 ± 0.1	0.892
Years after program-end[b] (years)	5.8 (3.8–8.6)	7.2 (5–8.6)	< 0.001

Data presented as mean ± SD, [a]Data presented as number (percentage), [b]Data presented as median (min, max)
Abbreviations: BMI = body mass index; %W/H = percentage weight-for-height

(dietary control and regular exercise) during the year preceding the long-term follow-up study, 11 (78.6%) were in the successful group. Four participants (9.3%) received continuing health follow-ups at our institute; 3 (75%) of those were in the failed group. In the case of the successful group, more participants continued with healthy lifestyles than those who did not continue healthy lifestyles nor receive treatment, or who continued to receive follow-up at our institute (p = 0.001). A logistic regression analysis showed that continuing healthy lifestyles was associated with weight-control success (OR 14.67, p < 0.001).

Nineteen participants with increased %W/H had blood tests to evaluate metabolic complications (19 had HbA1c; 18 had BS, 17 had lipid profiles, and 15 had ALT and AST). Ten successful-group participants also

TABLE 2. Comparison of clinical characteristics of participants at the end of the group-based program and at long-term follow-up.

	At program-end	At long-term follow-up	*P*-value
Age (years)	13.2 ± 2.2	19.2 ± 2.2	< 0.001
Percentage weight-for-height (%)	167.2 ± 32.8	180.9 ± 52.9	0.012
BMI (kg/m^2)	31.9 ± 6.5	35.2 ± 10.1	0.002
Waist[a] (cm)	95.0 ± 13.8	102.4 ± 21.8	0.003
Waist-height ratio[a]	0.59 ± 0.1	0.61 ± 0.1	0.164
Systolic blood pressure[a] (mmHg)	118 ± 12	127 ± 13	< 0.001
Diastolic blood pressure[a] (mmHg)	67 ± 9	78 ± 12	< 0.001

Data presented as mean ± SD, [a]n = 37
Abbreviation: BMI = body mass index

TABLE 3. Comparison of characteristics and factors affecting obesity control of the "failed" and "successful" groups.

	Failed group n = 26	Successful group n = 17	*P*-value
Male, person[a]	14 (53.8)	8 (47.1)	0.663
Age (years)	19.6 ± 2.2	18.5 ± 2.1	0.127
Weight (kg)	112.5 ± 29.8	76.1 ± 13.2	< 0.001
Height (cm)	166.7 ± 9.4	166.7 ± 7.0	0.978
BMI (kg/m^2)	40.2 ± 9.4	27.4 ± 4.9	< 0.001
%W/H (%)	207.5 ± 48.9	140.1 ± 26.6	< 0.001
Difference in %W/H between program-end and the long-term follow-up	36.3 ± 22.9	-20.8 ± 13.2	< 0.001
Exercise frequency (days/week)	2.9 ± 2.7	4.7 ± 2.0	0.018
Exercise duration[b] (min/week)	110 (0, 900)	240 (80, 1890)	0.006
Sleeping duration (hours/day)	7.7 ± 1.3	7.6 ± 1.1	0.780
Time spent on TV and internet (hours/day)	5.6 ± 3.1	4.2 ± 2.9	0.149
Number of meals daily	2.9 ± 0.4	2.8 ± 0.4	0.849

Data presented as mean ± SD, [a]Data presented as number (percentage), [b]Data presented as median (min, max)
Abbreviations: BMI = body mass index; %W/H = percentage weight-for-height

sought blood testing (10 had BS and lipid profile; and 9 had HbA1c, AST, and ALT). The results, detailed in Table 4, revealed increased FBS, ALT, total cholesterol, LDL-cholesterol, and HDL-cholesterol levels (p = 0.002, 0.031, 0.001, 0.041, and 0.003, respectively). The comparison of biochemical data between the failed-group participants and successful-group participants was shown in Table 5. Failed-group participants had higher levels of FBS and ALT and lower level of HDL-cholesterol (p = 0.005, p = 0.012, p = 0.002, respectively).

TABLE 4. Comparison of biochemical data at the end of the group-based program and at long-term follow-up.

	At program-end	At long-term follow-up	*P*-value
FBS (mg/dl; n = 28)	85 (71–96)	91 (76–209)	0.002
HbA1c (%; n = 28)	5.6 (4.8–6.2)	5.5 (4.5–8.9)	0.120
Triglyceride (mg/dl; n = 27)	84 (33–315)	93 (37–314)	0.869
Total cholesterol[a] (mg/dl; n = 27)	163.4 ± 28.3	180.3 ± 29.4	0.001
HDL-cholesterol[a] (mg/dl; n = 27)	45.6 ± 7.9	53.8 ± 14.0	0.003
LDL-cholesterol[a] (mg/dl; n = 27)	97.7 ± 24.2	106.2 ± 29.4	0.041
AST (U/L; n = 24)	19 (12–60)	20 (14–58)	0.884
ALT (U/L; n = 24)	17 (8–69)	23 (12–108)	0.031

Data presented as median (min-max), [a]Data presented as mean ± SD

Abbreviations: FBS = fasting blood sugar; AST = aspartate transaminase; ALT = alanine transaminase; HbA1c = hemoglobin A1c; HDL-cholesterol = high-density lipoprotein cholesterol; LDL-cholesterol = low-density lipoprotein cholesterol

TABLE 5. Comparison of biochemical data between the "failed-group participants" and "successful-group participants" at the long-term follow-up study.

	Failed-group participants	Successful-group participants	*P*-value
FBS (mg/dl)	93 (83–209) [n=18]	83 (76–94) [n=10]	0.005
HbA1c (%)	5.5 (4.7–8.9) [n=19]	5.2 (4.5–5.9) [n=9]	0.236
Triglyceride (mg/dl)	95 (48–314) [n=17]	74 (37–122) [n=10]	0.075
Total cholesterol[a] (mg/dl)	182.3 ± 30.6 [n=17]	182.1 ± 31.0 [n=10]	0.881
HDL-cholesterol[a] (mg/dl)	46.6 ± 11.0 [n=17]	64.4 ± 13.2 [n=10]	0.002
LDL-cholesterol[a] (mg/dl)	111.9 ± 23.2 [n=17]	102.0 ± 39.6 [n=10]	0.415
AST (U/L)	20 (14–58) [n=15]	18 (14–29) [n=9]	0.324
ALT (U/L)	33 (15–108) [n=15]	16 (12–50) [n=9]	0.012

Data presented as median (min-max), [a]Data presented as mean ± SD

Abbreviations: FBS = fasting blood sugar; AST = aspartate transaminase; ALT = alanine transaminase; HbA1c = hemoglobin A1c; HDL-cholesterol = high-density lipoprotein cholesterol; LDL-cholesterol = low-density lipoprotein cholesterol

At program-end, the 43 participants had these obesity complications: impaired glucose tolerance, 6 (14.0%); T2DM, 1 (2.3%); dyslipidemia, 17 (39.5%), comprised of hypertriglyceridemia, 6 (14%), low HDL-cholesterol, 11 (25.6%), and high LDL-cholesterol, 5 (11.63%); elevated transaminases, 1 (2.3%); and hypertension, 4 (9.3%).

In this long-term follow-up study, 28 had FBS performed; 3 (10.7%) had T2DM, comprising 2 new cases plus 1 case diagnosed during the group-based treatment program. The three were: 1) a 20-year-old female, with %W/H of 225.5% and a 48.9-kg weight gain over 7 years 4 months; 2) a 21-year-old female, who had had impaired

glucose tolerance during the group-based treatment program, with %W/H of 221.3% and a 21.5-kg weight gain over 5 years; and 3) a 22-year-old male, diagnosed with T2DM during the group-based treatment program, with %W/H of 254.1% and a 38.7-kg weight gain over 5 years 9 months. All three belonged to the failed group, had family histories of diabetes, and did not consistently control their diets or exercise before this study.

Four out of the 37 participants (10.8%) had elevated blood pressure; 3 were from the failed group. One failed-group participant had newly-found elevated blood pressure. All four had a family history of hypertension. Out of 27 participants tested for lipid profiles, 9 (33.3%) had dyslipidemia (hypertriglyceridemia, 3; low HDL-cholesterol, 4; and high LDL-cholesterol, 5), with 7 from the failed group, including 1 new case. Only 1 successful-group participant had newly-found high LDL-cholesterol. Out of 24 participants tested for liver function, 7 (29.2%) had elevated transaminases; 6 from the failed group included 5 new cases. Only 1 successful-group participant had newly-found elevated transaminases.

DISCUSSION

During 2006-2011, 115 obese children and adolescents participated in a 1-year, group-based treatment program focusing on healthy lifestyles and parental involvement.[6] Forty-three (37.4% of the initial subjects) enrolled in this subsequent, cross-sectional, follow-up study. Overall, they demonstrated an increased degree of obesity, with a median of 5.8 years after the program ended. However, 40% maintained their weight loss.

Weight-reduction programs involving more intensive therapy were reported to be successful at long-term weight maintenance.[7-9] An intensive program involving parents by Reinehr et al. resulted in sustained weight reduction for most participants 3 years after program-end.[7] This "Obeldicks" program comprised a 3-month intensive phase, with patients attending 6 group sessions and parents 6 evening sessions; a 6-month establishing phase, with individual, monthly, psychological family therapy given; and a late phase, with individual care if necessary. Moreover, weekly exercise therapy was provided for 12 months.[11,12] Participants were monitored annually up to 3 years following intervention-end; a BMI-SDS (BMI-standard deviation score) change during the first 3 intervention months was related to a BMI-SDS change 3 years after intervention-end.[7]

Following patients for 8 years, another study by Moens et al. found successful weight-reduction maintenance for most participants.[8] Focusing on healthy eating habits, moderate exercise, and cognitive-behavioral techniques, the intervention comprised 12-16 sessions during 3 phases: screening and motivation (2 sessions, 3 weeks); intensive treatment (6 biweekly sessions, 12 weeks); and follow-up (4-8 monthly meetings). At 8-year follow-up, participants had an 8% adjusted-BMI reduction, and 66% of children maintained weight control. The authors found long-term weight loss was positively associated with age, baseline BMI, and child's self-worth, but negatively associated with mother's poor mental health.[8]

The Combined DAK Therapy, an intensive, 1-year, weight-reduction intervention utilizing inpatient and outpatient treatment sessions, demonstrated weight reductions at 3- and 5-year follow-ups.[9] During the first 6 weeks, a multidisciplinary team provided inpatient, obese children and adolescents with structured, behavioral therapy. Over the subsequent 10.5 months, the participants had 11, one-hour, outpatient sessions for nutritional and physical-activity education, and behavioral therapy.[13] Five-year follow-up found a significant decrease in BMI-SDS from baseline (-0.15 ± 0.51, $p < 0.001$). Altogether, 26% saw BMI-SDS reductions (21.3% with successful weight reduction [a BMI-SDS decrease of ≥ 0.2], and 4.7% with a BMI-SDS reduction < 0.2).[9]

The aforementioned programs differ from ours in several ways. Firstly, our group-session frequency was much lower. This may partly explain the unsuccessful, long-term weight reduction displayed by 60% of our participants. Limited resources meant we could only provide 5 group-based sessions. However, we admitted patients for several days at program-commencement for lifestyle-modification education. The infrequent sessions may have impeded lifestyle changes in all patients, resulting in failure to develop long-term weight-control behaviors. Secondly, while psychological or cognitive behavioral therapy was provided by 3 other programs,[7-9] our program lacked such sessions. Psychotherapy could coach patients in positive-behavior development, weight-loss goal setting, weight-loss maintenance, and problem coping.[14]

In our study, 17 (39.5%) participants decreased or maintained %W/H (successful group) while 26 (60.5%) increased %W/H (failed group). The exercise frequency and duration were higher for the successful than the failed group. Participants who maintained reduced weight exercised 4.7 days/week (median: 4 hours/week) versus the failed group's 2.9 days/week (duration: 1.8 hours/week). Furthermore, consistent exercise and food control were associated with weight-control success: 11 (64.7%) of successful-group participants maintained healthy lifestyles through regular exercise and diet control during the year preceding the long-term follow-up study.

Other studies have found dietary control and physical activity benefit weight-loss maintenance.[15,16] Mirza et al. reported that intensive dietary control in the form of both low glycemic loads and low-fat diets resulted in weight reduction in obese children at 2-year follow-up.[15] In a cluster-randomized controlled trial, Donnelly et al. studied the effects of physical activity on weight control over 3 years in elementary school-children.[16] Ten schools (713 participants) were the control, while 14 schools (814 participants) were assigned to Physical Activity Across the Curriculum (PAAC). PAAC promoted 90 minutes/week of moderate-to-vigorous, physically active academic lessons, plus 60 minutes/week of physical education. PAAC exposure affected BMI: schools with ≥ 75 minutes of PAAC/week showed significantly lower BMI increases at 3 years than schools with < 75 minutes/week.[16] The results of those studies[15,16] and ours confirm that exercise and dietary control significantly impact long-term weight control.

By completion of our 1-year group-based treatment program, obesity complications had fallen.[6] At program-commencement, 23 participants were prediabetic, 2 had T2DM, and 65 had dyslipidemia. At program-end, there were 13 prediabetic participants (reduction: 43.5%); no new T2DM cases; and 48 dyslipidemia cases (reduction: 26.2%).[6] However, at long-term follow-up, 2 patients with massive weight gain had T2DM (one already had impaired glucose tolerance at program-end). For patients at risk (positive family history of T2DM and/or inability to achieve weight loss), psychotherapy might induce the motivation and long-term behavioral changes were needed to establish healthy lifestyles. Evaluation of underlying psychological disorders or stress should also be performed for individuals with pronounced weight gain.

Other obesity-related complications were common in the failed group. Newly-found disorders were high blood pressure and dyslipidemia (1 participant each), and elevated liver enzymes suggesting non-alcoholic steatohepatitis (5 participants). Our findings highlight the importance of effective childhood obesity-management because youth obesity is associated with increased adult mortality from obesity-related complications.[3,17]

The small number of participants in the long-term follow-up study is a limitation. Although the non-participants and 43 participants had similar profiles (age at first presentation and obesity degree), the long-term weight-control findings might not represent the whole group. Moreover, patients unable to attend hospital were interviewed telephonically.

Overall, this study revealed that the 1-year group-based treatment program did not achieve long-term weight reductions for most patients and was less intensive than more successful interventions. Resource limitations precluded the provision of psychotherapy, booster education, and annual follow-ups. However, 40% of participants maintained weight around 5 years after program-end. Continued healthy lifestyles, and frequent and longer-duration exercise were associated with successful weight maintenance. To achieve long-term weight maintenance, a more intensive weight-loss program with frequent sessions, psychotherapy, and annual follow-ups or continuous contact and support (e.g., by telephoning or messaging) might ensure sustained weight loss.

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Effect of a Goal Attainment Nursing Program on Self-management and Blood Pressure Control in High-risk Hypertensive Patients in a Primary Care Unit

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ABSTRACT

Objective: To determine the effects of goal attainment in nursing programs among hypertensive patients who are at high-risk to cardiovascular disease.

Methods: A quasi-experimental study was conducted in a primary care unit setting. Eligible participants included hypertensive patients aged 35 years and above with poorly controlled blood pressure and accompanying risk factors for cardiovascular disease. Seventy-eight participants were divided evenly into two groups via simple random sampling. The experimental group participated in a 10-week program consisting of small group education/demonstration sessions focused on goal setting and self-management behavior. These participants also received a follow-up phone call and text messages that served as reminders/reinforcements. The control group received routine care only, which included appropriately consultation with health care providers.

Results: The proportion of participants who achieved optimal blood pressure control (SBP < 140 mmHg) in the experimental group (80.6%) was greater than the control group (44.1%) (p-value < 0.05). In addition, the systolic blood pressure of the experimental group ($\bar{x}$ 131.33 mmHg, S.D. 12.09) was significantly lower than that of the control group ($\bar{x}$ 142.96 mmHg, S.D. 15.77) (p-value < 0.05). The mean scores for self-management behavior were significantly higher in the experimental group ($\bar{x}$ 106.14, S.D. 14.43) than the control group ($\bar{x}$ 83.21, S.D. 8.17) (p-value < 0.05).

Conclusion: The goal attainment nursing program targeting behavior modification through empowerment was effective in improving self-management behavior among hypertensive patients at high risk for cardiovascular disease. Thus, this program can be applied to patients with uncontrolled chronic diseases.

Keywords: Self-management; hypertension; cardiovascular disease; goal attainment; behavior modification (Siriraj Med J 2020; 72: 140-150)

INTRODUCTION

Cardiovascular disease (CVD) is the world leading cause of death claiming roughly 17.9 million per annum. In view of this staggering statistic, the World Health Organization supports governments worldwide in preventative efforts.[1] Hypertension is a significant risk factor for CVD. There is broad evidence from longitudinal observational studies and meta-analyses of RCTs that

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the BP-related risk for CVD is determined by systolic blood pressure (SBP) of approximately 115 mmHg.[2] In previous findings, the majority of CVD events presented in patients with blood pressure (BP) > 140/90 mmHg. However, more recent studies have found that most CVD events occur in patients with BP < 140/90 mmHg. Similarly, according to a study conducted in the early 2000s, hypertension can lead to CVD events with coronary heart disease at 63 percent, stroke at 63 percent and heart failure 60 percent.[3] This illustrates the need for early detection and management of high-risk hypertensive patients to avoid CVD complications.

Lifestyle factors that lead to increased risk for CVD are well-known (poor diet quality, physical inactivity, tobacco use, increased blood pressure). Prevention programs often seek to address these factors through education and behavior modification. Interventions that have proven effective in combating hypertension include education on the aforementioned risk factors, physical activity with aerobic exercise and implementation of a DASH diet (limiting sodium consumption to less than 2,300 mg daily).[4-6] Regular blood pressure monitoring and medication adherence are also important for disease control.[7-9] Based on RCT evidence, hypertensive patients with systolic blood pressure of 130-139 mmHg who are at high risk for CVD should receive both lifestyle modification and BP-lowering medication.[2]

A previous study found that blood pressure (BP) self-monitoring resulted in lower systolic blood pressure. There is promise in interventions promoting self-management behavior in achieving proper BP control to lower the incidence of cardiovascular disease.[8] More research is needed to evaluate the benefits of group education programs with assessment of risk factors and information on lifestyle modification. Further studies are also required to determine optimal ways to overcome the barriers to engagement between patients and providers in these programs.[10] Home blood pressure (HBP) monitoring with weekly telephone follow-ups can effectively track measurements. In addition, telephone consultation is also useful in tracking HBP related to BP control. In this way, health providers can easily follow patients' BP at home.[7,23] Thus, interventions can also undertake a technology-mediated approach for ancillary follow-up with tele-counseling or tele-monitoring.[11]

In this study, a 10-week goal attainment nursing program was designed for hypertensive patients at high-risk for CVD at a primary care unit in Siriraj Hospital. Empowerment and self-management of hypertension were the fundamental elements of the program. The study aimed to determine the effects of the program on self-management behavior to prevent cardiovascular disease and decrease systolic blood pressure.

MATERIALS AND METHODS

Research Design

The present study was a quasi-experimental research with two groups in a pretest-posttest design conducted at a primary care unit (Siriraj Hospital) in Bangkok, Thailand, from May to August 2018.

Participants

Hypertensive individuals with follow-up appointments between May and August 2018 were recruited.

Inclusion Criteria:

1. Diagnosis of hypertension at least six months prior to the study
2. SBP over 130 mmHg and/or DBP over 85 mmHg
3. Prescription of at least one antihypertensive drug
4. At least one of the following additional cardiovascular risk factors:
    a) Family history of CVD
    b) Smoking
    c) Diagnosis with DM
    d) Hyperlipidemia (any of the following: total cholesterol > 200 mg/dL, triglycerides > 150 mg/dL, low-density lipoprotein > 130 mg/dL, high-density lipoprotein < 40 mg/dL)
    e) Overweight (body mass index > 25 kg/m^2 or waist circumference > 90 cm in males and > 80 cm in females)[12]
5. Personal mobile phone; Thai language literacy

Exclusion Criteria:

1. Pre-existing cardiovascular complications
2. Referral to special treatment without returning to the primary care unit

Sample Size Calculation

The researchers used the effect size of a previous study based on systolic blood pressure outcome.[13] The calculation showed that d is 1.24, which is higher than 0.8 and a good effect size.[14] The sample size for the present study was derived through power analysis (alpha = 0.05 with 80% power). The G power program (Version 3.1.9.2)[15] determined that the total sample size should be 70 people. In this study, the researchers increased the sample size by 10 percent to account for the drop-out rate. Thus, 78 participants were subsequently and evenly divided into the experimental and control groups by simple random sampling.

Ethics

This study was approved by the Human Research Protection Unit, Faculty of Medicine Siriraj Hospital at Mahidol University, Bangkok, Thailand (Si 201/2018). The protocol number is 079/2561(EC4), and all participants signed informed consent forms. (TCTR identification number: TCTR20190402001)

Recruitment

Eligible participants were screened from electronically recorded data (Medtrack system). The participants successfully recruited in odd-numbered weeks were assigned to the experimental group via simple random sampling; those recruited in even-numbered weeks were assigned to the control group.

Patients were invited to participate in the study after blood pressure measurements had been taken. Then the objectives, duration, and risks involved in the study were explained. Confidentiality issues were also addressed. The subjects who agreed to participate then voluntarily completed and signed the consent forms. (Fig 1)

Intervention

Experimental Group

The researchers developed a 10-week goal attainment nursing program to prevent cardiovascular diseases in hypertensive patients. This program emphasized goal attainment and promotion of self-management behavior. The initial process began with interactions to identify the barriers and common health problems with information about CVD risk factors. The program then created goals for the patients. Implementation of the aforementioned goals led to encouraging self-monitoring, recording and evaluating of goals. The difficulties and physical outcomes were tracked and supported for ten weeks via telephone follow-ups. At the last session, the patients received feedback on behavior modification and evaluation of goal achievement in a discussion group.

All of these processes improved the continued interactions between nurses and patients. The program included two education sessions in a small group, two follow-up text message reminders, and a 10-minute personal follow-up telephone call. During the group education sessions, activities were conducted in each sub-group of 4-6 patients. (Table 1)

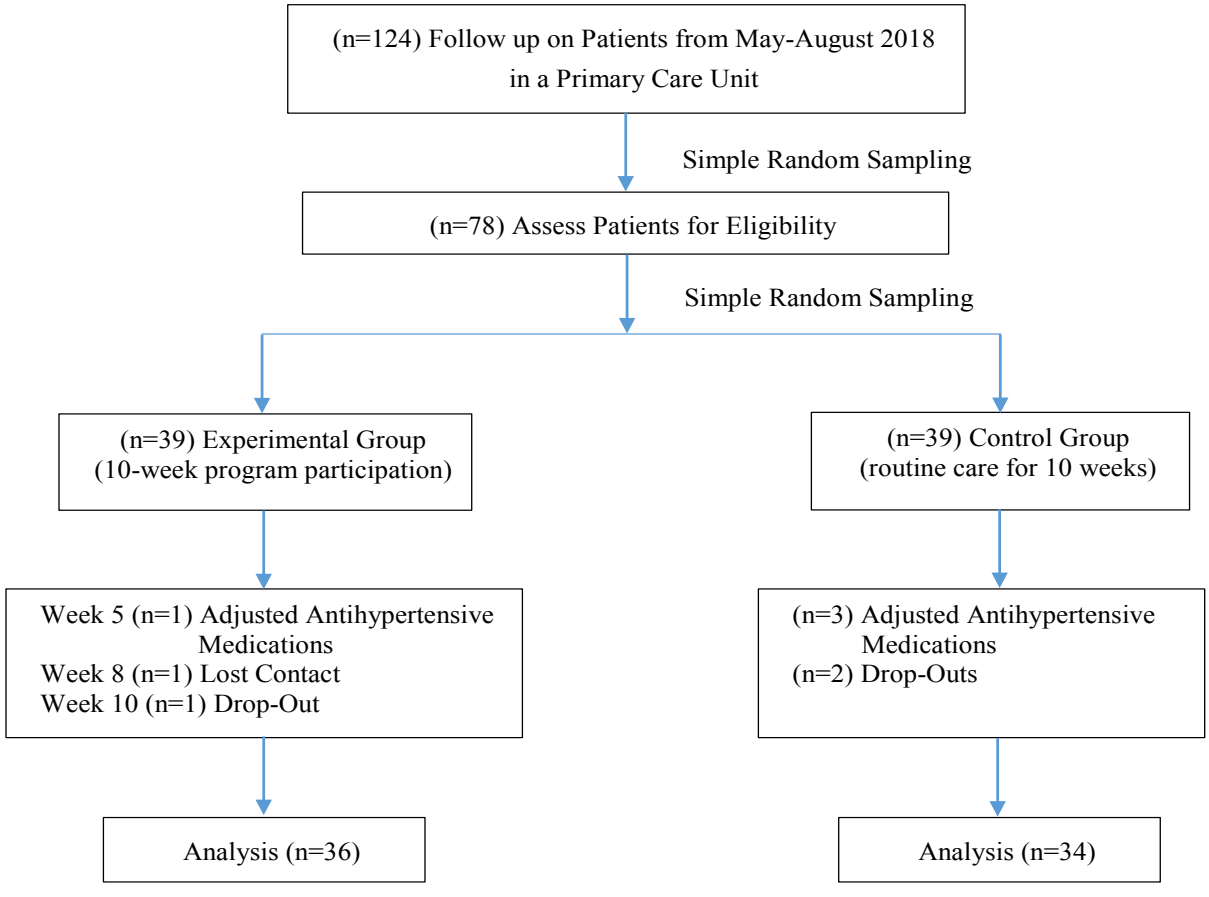

Fig 1. Flow Chart of Research Process.

TABLE 1. Program activities.

Session	Purpose	Activities
Week 1		
Nurse-patient interaction process (30 minutes)	1. To build rapport and share information on health problems.	**Sub-group small-talk** - Patients reveal individual obstacles to controlling disease.
Collaborative goal-setting process (2 hours)	1. To collaborate on setting goals for behavior modification.	**Sub-Group Education** - Lecture on CVD risks, provision of adequate information using the PowerPoint program, video content and a guidebook developed by the researchers. - Patients set short- and long-term goals by collaborating with the researchers. - Discussion about appropriate solutions on how to achieve set goals.
	1. To encourage self-management to facilitate patients in achieving behavior modification. 2. To provide essential information on CVD and how patients can improve completely for behavior modification.	**Sub-Group Education** - Coaching on self-management skills in various aspects including nutrition, exercise, compliance with hypertensive medication, avoidance of CVD risks and home-BP monitoring. - Practicing self-monitoring, evaluation and reinforcement by using handbooks to keep records. - Researchers guided patients on practical action to achieve short- and long-term goals.
Week 3		
Transaction process	1. To continue communication with patients by promoting constant behavior modification through text messages.	**Text reminders** are sent individually.
Week 5		
Transaction process	1. To follow progress towards established goals, and to address any potential barriers to change. 2. To track home-BP measurement and follow monitoring of goal achievement.	**Personal Follow-Up Telephone Calls:** (10 minutes per patient) by following a self-recorded handbook. - Researchers allow patients to reveal prideful feelings regarding reach optimal BP (<140/90 mmHg) and improve self-confidence on BP-control. - Barriers to behavior modification are clarified and solves with feasible methods to change former habits.
Week 7		
Transaction process	1. To continue communication with patients by promoting constant behavior modification through text messages.	**Text reminders** are sent individually.
Week 10		
Evaluating the goal achievement process (2 hours)	1. To reflect on changeable behaviors and BP control for the ten-week period. 2. To evaluate goal achievement: self-management behavior and physical outcomes. 3. To discuss health information, share obstacles and achievable behavior modification.	**Sub-Group Small-Talk** - Patients review goals and their respective accomplishments e.g. physical outcomes, alterations of self-management behavior. - Weekly self-recording on nutrition, exercise and blood pressure are reviewed and compared through participation in the program. - Researchers provide individualized feedback at the end of the session.

Control Group

During the 10-week sessions, patients received routine nursing care at the primary care unit, obtaining a self-management guidebook to prevent cardiovascular disease in the first week for self-study at home. At the end of the program, the patients received recommendations and five to ten minutes of individualized counseling on behavior modification.

Measurements

Part 1: Demographic Data

Demographic information on gender, age, marital status, religion, education level, occupation, and monthly income was obtained from all of the participants. Anthropometric indices (body weight and waist circumference) were collected at baseline. The baseline blood pressure (SBP, DBP) was collected pre- and post-program for comparison. The researchers also obtained participants' medical history for the duration of hypertensive illness, antihypertensive medications, comorbidities, CVD risks, alcohol consumption, smoking, and exposure to secondhand smoke.

Part 2: Self-Management Behavior for CVD Prevention

Lifestyle practices were evaluated by using a questionnaire on self-management behavior to prevent CVD with 35 items composed of dietary intake (11 items), physical activity (7 items), medication (5 items), avoidance of CVD risks (5 items) and home BP monitoring (7 items) with both positive and negative questions. The questionnaire was developed based on the literature review of research on the following topics: 1) self-management promotion program for health behavior in hypertensive patients[16]; 2) self-management behavior questionnaires[17] and 3) medication adherence questionnaires.[18] The responses were rated on 4-point scales by which the participants indicated frequency of consumption by choosing only one category. The frequency was categorized from 1 (never) to 2 (1-2 times/week), 3 (3-4 times/week) and 4 (5-7 times/week). The total scores ranged between 35 - 140 points and Cronbach's alpha coefficient for this questionnaire was 0.81.

Blood Pressure Measurement

BP was measured with a GE Carescape V100 Vital Signs Rolling Stand Monitor. The participants were required to sit and rest for five minutes prior to BP measurement. BP was then measured twice over a period of one minute on the left arm, and the average BP was calculated.

Statistical Analysis

SPSS statistics software (Version 18) was used for data analysis. The significance level was set at .05 by using descriptive statistics (frequency, percentage, mean and standard deviation) for the presentation of the demographic data. Subsequently, a Chi-square test was used for comparison between the experimental and control groups.

Within-group differences in the mean systolic blood pressure and self-management behavior scores were analyzed both pretest and posttest with paired *t*-test; the between-group differences of these markers were analyzed with independent *t*-test. The Kolmogorov-Smirnov Test was used for normality testing for baseline data between the two groups.

RESULTS

Thirty-six subjects remained in the experimental group at the end of the study (attrition rate = 7.7%). One subject was not able to participate in the activities, one patient was prescribed changes in antihypertensive medications, and contact was lost with one patient. Thirty-four subjects remained in the control group (attrition rate = 12.8%). Three subjects were prescribed to new antihypertensive medications, and two patients could not attend the follow-up appointment. Overall, the total attrition rate was 10.3 percent.

There were differences in gender distribution across both groups; 75 percent of the experimental group was female versus 50 percent in the control group. Furthermore, the mean age of the patients in the experimental group was 61.47 (±6.33) years, and the mean age in the control group was 65.29 (±8.42) years. The other demographic characteristics of the experimental and groups showed no statistically significant differences (marital status, religion, education level, employment status, income level) (Table 2).

Both groups had similar health characteristics such as body weight, waist circumference and systolic and diastolic blood pressure prior to participation in the study. The antihypertensive agents prescribed for the participants included diuretics, calcium channel blockers, angiotensin-converting enzymes, angiotensin receptor blockers, beta-blockers and vasodilators with similar prescription among the hypertensive patients in both groups. The groups had similar prevalence of CVD risk behaviors (alcohol consumption, smoking, and secondhand smoke exposure). The majority of the participants in both groups had a total of three CVD risk factors (41.7% in the experimental group, 50.0% in the control group) (Table 3).

TABLE 2. Demographic data of the experimental and control groups.

Characteristics	Experimental Group n (%)	Control Group n (%)	*P*-value
Gender			0.030[a]
Male	9 (25.0)	17 (50.0)	
Female	27 (75.0)	17 (50.0)	
Age			0.035[b]
35-59 years	12 (33.3)	9 (26.5)	
≥ 60 years	24 (66.7)	25 (73.5)	
	($\bar{x}$ = 61.47, S.D. = 6.33, Min = 50, Max = 71)	($\bar{x}$ = 65.29, S.D. = 8.42, Min = 38, Max = 79)	
Marital Status			0.782[a]
Single/Widowed/ Divorced	16 (44.4)	14 (41.2)	
Married	20 (55.6)	20 (58.8)	
Buddhism	36 (100.0)	34 (100.0)	
Education Level			0.352[a]
Lower than secondary school	26 (72.2)	21 (61.8)	
Higher than secondary school	10 (27.8)	13 (38.2)	
Occupation			0.989[a]
Unemployed	19 (52.8)	18 (52.9)	
Employed/business owner/ Farming/sewing	17 (47.2)	16 (47.1)	
Monthly income			0.355[b]
Less than/as 5,000 Baht	21 (58.3)	22 (64.7)	
More than 5,000 Baht	15 (41.7)	12 (35.3)	

[a] = Chi-square testing; [b] = *t*-test

Self-Management Behavior for CVD Prevention

The experimental group had significantly higher mean self-management behavior scores as compared to the control group (106.14, S.D. 14.43 VS 83.21, S.D. 8.17) (p-value < 0.05). Differences were reflected in the mean scores for dietary intake (p-value < 0.05), physical activity (p-value < 0.05), avoidance of CVD risk factors (p-value < 0.05), and home blood pressure monitoring (p-value < 0.05) (Table 4).

Systolic Blood Pressure

Posttest, the mean systolic blood pressure was 131.33 mmHg (S.D. 12.09) in the experimental group and 142.96 mmHg (S.D. 15.77) in the control group. Analysis with independent *t*-test revealed the aforementioned differences to be significant (p-value < 0.05). In addition, the experimental group experienced a greater decrease in systolic blood pressure than the control group (91.7% vs. 70.6%) (p-value < 0.05). More participants in the experimental group achieved optimal systolic blood pressure control (< 140 mmHg) than the control group (80.6% VS 44.1%, p-value < 0.05) (Table 5).

Furthermore, after the participants had taken part in the goal attainment program for ten weeks, the researchers compared the patients who were under blood pressure control in both groups. Optimal or acceptable systolic and diastolic blood pressure levels were defined to interpret who was able to achieve blood pressure control. According to the findings, the experimental group (50.0%) had more patients with blood pressure under 130/80 mmHg than in the control group (20.6%). Moreover, there were also more patients who had achieved blood pressure control at posttest (50.0%) than at pretest (2.8%) in the experimental group (Fig 2).

TABLE 3. Health information of the experimental group and control groups.

Health Information	Experimental Group n (%)	Control Group n (%)	*P*-value
Body Weight			0.879[a]
($\bar{x}$ = 68.75, S.D. =12.03, min=51.40, max=120.00)		($\bar{x}$ = 69.22, S.D. =13.79, min=43.00, max=107.00)	
Waist Circumference			0.143[b]
Normal	3 (8.3)	7 (20.6)	
Over (Male> 90 cm, female> 80cm)	33 (91.7)	27 (79.4)	
Baseline Systolic Blood Pressure			0.269 [a]
130 – 140 mmHg	10 (27.8)	11 (32.4)	
> 140 mmHg	26 (72.2)	23 (67.6)	
($\bar{x}$ = 153.15, S.D.=14.47, min=130.00, max=197.00)		($\bar{x}$ = 149.24, S.D.=14.91, min=130.00, max=196.00)	
Baseline Diastolic Blood Pressure			0.415[a]
≤ 80 mmHg	32 (89.0)	29 (85.3)	
81 – 90 mmHg	2 (5.5)	4 (11.8)	
> 90 mmHg	2 (5.5)	1 (2.9)	
($\bar{x}$ = 75.07, S.D. = 8.08, min = 62.00, max = 101.50)		($\bar{x}$ = 73.38, S.D. = 9.13, min = 60.00, max = 94.00)	
Duration of Hypertensive Illness			0.376[a]
≤ 10 years	26 (72.2)	18 (52.9)	
> 10 years	10 (27.8)	16 (47.1)	
($\bar{x}$ = 8.69, S.D. = 4.18, min = 2, max = 16)		($\bar{x}$ = 9.68, S.D. = 5.02, min = 2, max = 20)	
Anti-Hypertensive Drugs*			
Diuretics	3 (8.3)	7 (20.6)	
Calcium channel blockers (CCBs)	24 (66.7)	25 (73.5)	
Angiotensin Converting Enzymes Inhibitors (ACEIs)	14 (38.9)	18 (52.9)	
Angiotensin receptor blockers (ARBs)	16 (44.4)	9 (26.5)	
Beta-blockers	16 (44.4)	12 (35.3)	
Vasodilators	11 (30.6)	11 (32.4)	
History of Illness			0.282[b]
Only Hypertension	9 (25.0)	5 (14.7)	
Hypertension with co-morbidity	27 (75.0)	29 (85.3)	
Diabetes Mellitus	6 (22.2)	10 (34.6)	
Hyperlipidemia	9 (33.3)1	3 (44.8)	
DM with Hyperlipidemia1	2 (44.5)	3 (10.3)	
Glaucoma/Gout/Malignant Neoplasm of Breast	0 (0.0)	3 (10.3)	
CVD Risks			
2 Factors	6 (16.7)	11 (32.4)	
3 Factors	15 (41.7)	17 (50.0)	
4 Factors	13 (36.1)	5 (14.7)	
5 Factors	2 (5.6)	1 (2.9)	
Alcohol Consumption			0.498[b]
No	32 (88.9)	30 (88.2)	
Yes	4 (11.1)	4 (11.8)	
Smoking			0.204[b]
No	35 (97.2)	31 (91.2)	
Yes	1 (2.8)	3 (8.8)	
Secondhand Smoke Exposure			0.932[b]
No	32 (88.9)	30 (88.2)	
Yes	4 (11.1)	4 (11.8)	

[a] = *t*-test, [b] = Chi-square testing

* = Patients may take more than one drug per person

TABLE 4. The results of self-management behavior for prevention of CVD between the experimental and control groups at pre- and posttest.

Self-Management Behavior for Prevention of CVD	Pretest			Posttest		
	Experimental Group mean (SD)	Control Group mean (SD)	*P*-value	Experimental Group mean (SD)	Control Group mean (SD)	*P*-value
Total scores	78.08 (9.43)	79.24 (7.95)	0.583	106.14 (14.43)	83.21 (8.17)	<0.001
Dietary	22.31 (5.12)	21.82 (3.22)	0.637	29.83 (5.17)	22.68 (3.34)	<0.001
Physical activity	10.72 (3.41)	11.44 (4.33)	0.442	17.89 (5.38)	11.85 (3.38)	<0.001
Medication adherence	16.78 (2.03)	17.62 (2.05)	0.089	18.11 (2.86)	17.97 (1.78)	0.805
Avoidance of CVD risks	15.72 (1.81)	15.24 (2.38)	0.337	17.39 (2.20)	16.35 (2.09)	0.047
Home-BP monitoring	12.56 (3.30)	13.12 (2.46)	0.424	22.92 (4.33)	14.35 (2.60)	<0.001

Independent *t*-test

TABLE 5. Results on changes in systolic blood pressure between the experimental and control groups at the pre- and posttest.

Achievement of SBP Control	Experimental Group n (%)	Control Group n (%)	*P*-value
Pretest			0.114
Controlled (130-139 mmHg)	5 (13.9)	10 (29.4)	
Uncontrolled (≥140 mmHg)	31 (86.1)	24 (70.6)	
Posttest			
Controlled (<140 mmHg)	29 (80.6)	15 (44.1)	0.002
uncontrolled (≥140 mmHg)	7 (19.4)	19 (55.9)	

Chi-square testing

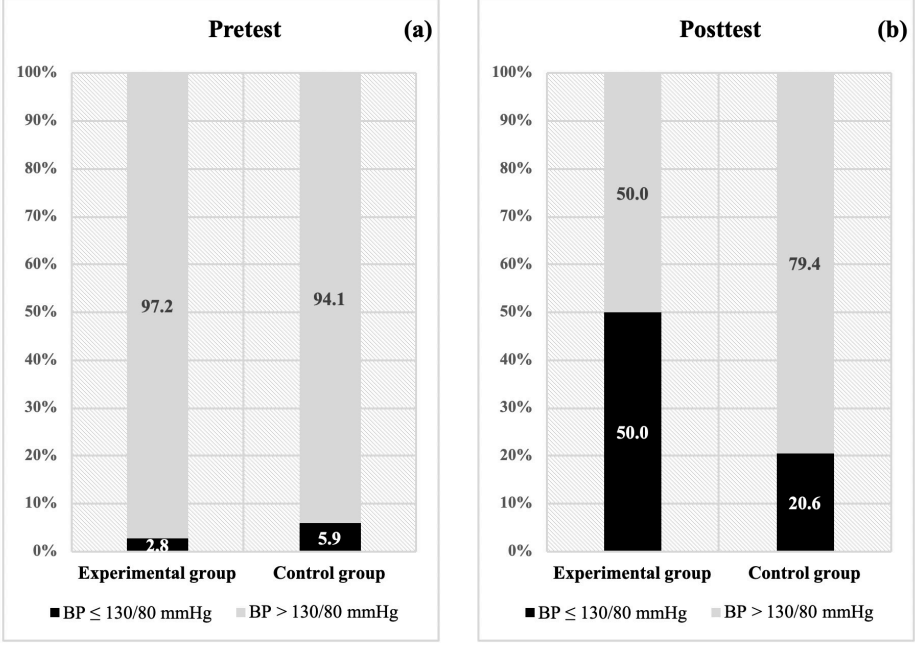

Fig 2. Bar charts illustrating blood pressure control at (a) pretest and (b) posttest in the experimental and control groups.

DISCUSSION

The mean score for the self-management behavior of the participants who took part in the 10-week goal attainment nursing program was significantly higher than that of the control group. A significant intragroup difference in pre-post mean scores was also noted in the experimental group (p-value < 0.05). Furthermore, the experimental group had a considerably higher likelihood to decrease systolic blood pressure than the control group (p-value < 0.05). These findings have positive implications.

Small-group educational activities that facilitated provider-patient interactions were particularly conducive to sharing experiences, perspectives and barriers to engaging in lifestyle changes. The findings are consistent with previous studies on programs for preventing complications in hypertensive patients through knowledge sharing and group discussions.[13,19,20]

During the goal attainment process, nurses provided guidance and feedback in group education. Essential knowledge about dietary intake, physical activity, medication, avoidance of CVD risks and home-BP monitoring were the topics of the lectures. Nurses trained patients by performing demonstrations on self-management: self-assessment, self-monitoring, and self-reinforcement. The most important aspect of the goal attainment process is understanding between nurses and patients. Patients play a role in assessing personal capability and limits in behavior modification. At the same time, nurses repeatedly assess patients. Next, nurses move toward the negotiation step for setting reachable and practical goals. In the aforementioned process, when patients were trying to modify behavior at home, telephone communication was a virtual method for monitoring. Thus, text reminders and follow-up phone calls were given as reinforcements throughout the ten-week period.

The phone calls helped nurses to inquire about the obstacles and problems encountered in behavior modification. If patients were unable to accomplish set goals, this process allowed the nurses and patients to continually interact and share information. The nurses worked as facilitators in guiding patients to adopt more feasible methods. Furthermore, the nurses helped patients by suggesting the setting of more flexible goals such as talking to reduce the frequency of eating brown rice if the practice is not convenient for some meals. The researchers found the follow-up phone calls to build empowerment and self-confidence in patients. The text reminders and phone calls were able to prevent patients from giving up on behavior modification when they were about to fail. On the other hand, when patients are able to meet personal goals, the nurses would offer praise to build self-confidence. Eventually, effective communication helped the patients properly manage behaviors on their own. This activity can benefit healthcare providers in tracking patients immediately and easily while the patients are at home.

According to the World Health Organization, blood pressure should be controlled at less than 130/80 mmHg[2]. Based on the above standard, the program implemented in the present study was effective. One of the reasons for successful achievement over a period of only ten weeks is that the program not only educated patients on essential CVD contents, but the researchers also guided patients on self-management for behavior modification on their own. From the start of the program, the patients needed to be able to assess potential for change in areas such as intention, ability, time and social support. Next, behavior plans were formed by collaborating with nurses in the goal-setting process. Additionally, when patients stayed at home, the nurses would stay in contact with them during the ten-week period. Therefore, teaching about self-management resulted in patients' ability to maintain blood pressure control (blood pressure < 130/80 mmHg).

The findings of the present study are consistent with the results of previous programs emphasizing behavioral goal-setting in combination with the support of a follow-up system.[21] Furthermore, the process in studies which applied the goal-setting to a primary care unit was effective in decreasing blood pressure.[22,24,25] The present study found that encouragement of blood pressure monitoring at home resulted in more effective blood pressure control. The above finding was found to be related to previous studies that trained patients to monitor blood pressure at home. In addition to taking blood pressure measurements, patients need to either record the measurements correctly in a handbook or send the BP readings to health care providers through electronic data sorting.[7,8]

In conclusion, providing interactions between nurses and patients during follow-up appointments at clinics promotes effective communication on goal-setting for behavior modification. In the beginning, and when goals are asserted clearly, patients can modify behavior in the right direction. Moreover, small group education offers more effective learning for patients by sharing information with one another, because small focus group discussions give patients more confidence about revealing personal information in a group setting than having face-to-face consultations with nurses. Furthermore, demonstrations of behavioral practices such as restricting sodium and fat

consumption, estimating daily recommended amounts of vegetables and planning to increase physical activity facilitate patients' comprehension of the content. In particular, BP-monitoring training helps patients learn about the physical outcomes of behavior modification. Teaching patients to read blood pressure levels from a device enables patients to interpret classification by using a color graph and recording in a handbook. Thus, BP-monitoring is beneficial for nurses in continuing to monitor patients' blood pressure management. In addition, follow-up phone calls allow health care providers to follow up on obstacles and blood pressure trends before the next appointment. Overall, the program implemented in the present study is effective in achieving blood pressure management, particularly in out-patient clinics.

Limitations

The findings of the present study show that the context of a program can decrease systolic blood pressure for participants at posttest. According to the demographics of the primary care unit, a 10-week goal attainment program is compatible with participants who routinely come for follow-up appointments every two to three months. This period can further present changes in lowering blood pressure as in previous studies. However, to promote adherence to maintenance of behavior modification, this program should be extended to interventions lasting at least six months based on behavior modification theory.

CONCLUSION

The hypertensive patients at high-risk for CVD who participated in the 10-week goal attainment nursing program for cardiovascular disease prevention (focused on self-management behavior) displayed significant improvement in achieving BP control. These results indicate that the experimental group had a larger decrease in systolic blood pressure than the control group (91.7% vs. 70.6%).

The findings of this study reveal the benefits of blood pressure control in patients by encouraging communication between nurses and patients on collaborative goal-setting. In particular, physical health in blood pressure was clearly stated from the start of the program. The role of the nurse in this program focuses on guidance regarding appropriate methods tailored for individual patients. Moreover, all goals need to be practicable and reachable for patients. This strategy accordingly leads to patients' success in behavior modification and effective blood pressure management. In addition, in the self-management process, nurses can promote the self-blood pressure monitoring of patients and follow up on obstacles during practice. Continuous blood pressure monitoring obviously presents noticeable trends and is easy for nurses to follow. Thus, nurses can continually promote empowerment through text and follow-up telephone calls. These certainly effect on building confidence in blood pressure control.

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Factors Influencing the Occurrence of Hand Foot and Mouth Disease Among Children in Day Care Centers in Northern Thailand

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ABSTRACT

Objective: Hand-foot-and-mouth disease (HFMD) is crucial and has a large-scale impact on worldwide healthcare systems in terms of expenses especially in the population of young children.

Methods: A community-based, case-control study was conducted to identify the factors influencing the occurrence of HFMD among children in day care centers (DCC). The study was conducted in three provinces in Northern Thailand including Chiang Rai, Chiang Mai, and Pha Yao. DCC and study samples were selected by a simple random method. A validated questionnaire was developed and used for collecting data after an index of item-objective congruence (IOC) method has been used to improve the quality of the questionnaire and piloted. Logistic regression was used to detect the associations between variables at the alpha =0.05.

Results: In total, 1,022 subjects were recruited into the analysis. Regarding parents' characteristics, 77.3% of the subjects were female, the average age was 33.9 years, 85.3% were married and 92.2% were Buddhist, 30.4% earned 5,001- 10,000 baht a month, and 49.9% had 1-3 family members. 17.9% had a low level of knowledge, 49.3% had a neutral attitude, and 96.7% had good practice for HFMD prevention and control. 34.2% of the children were aged ≤ 2 years, 54.9% were male, 50.4% were overweight and 21.1% had been breastfed. Three associated factors were found statistically significant with the occurrence of HFMD; children aged ≤ 2 years (OR=7.05, 95%CI=3.25–15.28), the number of household members (OR=1.43, 95%CI=1.04–1.97), and parents' knowledge (OR=2.35, 95C%= 1.47–3.77).

Conclusion: Improving knowledge of HFMD among the parents, particularly those having many household numbers, is essential in order to reduce the incidence of the disease.

Keywords: Hand foot mouth disease; day care center; associated factors; children (Siriraj Med J 2020; 72: 151-158)

INTRODUCTION

Hand foot and mouth disease (HFMD) is a common infectious disease[1,2] which is often reported in children under 6 years old particularly in tropical zones including Thailand.[3] HFMD is known to be a viral disease with limited specific treatment, but the number of infections has impacts on a global scale[4,5] and has defiantly become a public health challenge due to the cost of care, prevention, and control measures.[6,7] Most of HFMD infected patients come with mild signs and symptoms; however, some of them are in a severe stage of infection with brain and nervous systems complications.[2,8]

In Thailand, 70,077 cases were reported in 2017 (morbidity rate 107.57 per 100,000 pop.), and the three cases

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of reported death, were mostly children aged between 0-6 years[9,10] Northern region of Thailand had been announced as the highest epidemic area.[11] Meanwhile, Chiang Rai, Chiang Mai, and Pha Yao were ranked in top HFMD epidemic area in 2015.[12]

Health promoting hospitals are the peripheral health care center under the health care system of Thailand. A center is in a sub-district and responsible for more than 5,000 inhabitants.[3] These health care centers are delivering care by 2-3 health care professionals who are, for example, nurse, public health professional, etc. There are a few health care centers that have a medical doctor.[10] The limitation of the operation is that some of the centers are located far away from the city and received limited recourse each year. Therefore, the main duty of these centers is to treat their patients. A small budget is provided in health promotion and disease prevention including the control of HFMD outbreaks.

Chiang Rai, Chiang Mai, and Pha Yao are located in Northern Thailand which their typical mountainous characteristics, with lower average temperatures than other regions in Thailand for a whole year.[13] There are some hill tribe populations living in these areas with low economic status.[14] For this reason, in daytime, most parents leave their children in a day care center where care givers take care of the children. Many studies have shown that HFMD is associated with economic status.[15,16,17]

DCC, operated by the local government, is a place where children under 6 years are taken care of during the daytime.[11] Many people in rural area of Thailand prefer to leave their children at the DCC before going to the farm during the daytime. The numbers of children receiving care in some DCCs are higher than the standard of the Ministry of Public Health[3] and some DCCs became overcrowded.

There are several guidelines for HFMD control and prevention in Thailand and many health implementations have also been conducted under the supervision of the Ministry of Public Health of Thailand. However, there were many episodes of outbreaks reported throughout Thailand during the past years especially in Chiang Rai, Chiang Mai, and Pha Yao provinces. The study aimed to investigate the factors influencing HFMD in DCCs. The information might help develop the proper prevention and control measures to reduce the number of HFMD outbreaks in Northern Thailand.

MATERIALS AND METHODS

Study design

A community-based, case-control study was conducted to reveal the factors influencing HFMD among children under 6 years old who stayed in day care centers in Chiang Rai, Chiang Mai, and Pha Yao, Thailand.

Study site

The day care centers located in Chiang Rai, Chiang Mai, and Pha Yao were the study settings. In 2015, 1,345 DCCs in three provinces (Chiang Rai=499 DCCs, Chiang Mai=645 DCCs, and Pha Yao=199 DCCs) were examined. Using the median line of three years prior to 2015 (2012-2014) [Ministry of Public Health, 2016], 438 DCCs were marked as the high epidemic area, and 907 DCCs were marked as the low epidemic area.

Study population

The study population was the children aged less than 6 years and attended any DCC in 2015. However, the data was collected from their parents.

Study sample and sample size estimation

Case were children who were less than 6 years old and had been diagnosed with HFMD (ICD- 10: B08.4) in DCC by a medical doctor in 2015. The confirmation of the diagnosis was reviewed based on the medical record after obtaining the verbal approval from their parents. The selected samples that did not have the medical record on their diagnosis were excluded from the study. Controls were selected by a random method, from children who were less than 6 years old and had not been infected by HFMD in 2015 in the low epidemic DCC with a 1:2 ratio of the cases to controls.

The sample size was calculated using Schlessel man's formula[18] at alpha value 0.05, the power of test was set at 80%, and the ratio of cases to controls was 1:2, probability of exposure in case at 4.5%.[19] The ratio of the cases to controls was 1:2; therefore, 332 cases and 690 controls were required after adding 10% for any possible errors in the study.

Research instruments

The questionnaire was developed from reviewing the literature from all relevant sources of information. It consisted of three sections; general information, identification of infection risks, and assessment of knowledge, attitude, and practice (KAP). There were eighteen items for the general information section and 23 items for the identification of HFMD infection risks. In the KAP section, there were 10 items for knowledge, 10 items for attitude, and 10 items for practice.

The questionnaire had been tested for the validity and reliability by three external experts who had a relevant knowledge and experience in the field.[20,21] The quality

of the questionnaire also had been improved by being piloted with 20 selected samples from Mae Fah Luang University Hospital who had similar characteristics with the subjects in the study. Cronbach's alphas were calculated and found at 0.77 and 0.73 for attitude and practice respectively.

Process of data collection

The lists of DCCs were classified into two different groups; the high epidemic area and the low epidemic area by using the median of cases reported during 2012-2014. A list of DCCs were inserted into the same work-sheet and labeled with numbers.

A simple random method was applied to select the targeted DCCs for the high and low epidemic areas. There were 62 DCCs from the high epidemic area and 47 DCCs from the low epidemic area.

Cases were all the selected children who met the criteria, and controls, chosen by a simple random method, were the children from the same DCC where the cases were found but did not have HFMD.

The parents whose children had been selected as case or control were invited to the interview. A private room was prepared and used for the interview. The participants were given all essential information of the research including objective, rights, etc. Signed informed consent forms were obtained from each participant before the one-to-one interview which lasted 35 minutes.

Data analysis

The analyses were performed by using SPSS version 20, 2014 (SPSS, Chicago, IL), and Epi-Info version 6.04d (US Centers for Disease Control and Prevention, Atlanta, GA). Descriptive and inferential statistics were used to explain the characteristics and to answer the objective of the study. Logistic regression was employed to identify the associations between variables at the significant level alpha =0.05.

Ethical consideration

All study protocols were reviewed and approved by Mae Fah Laung University Ethics Committee on Human Research by No. REH-59024. Permissions to access the DCCs were granted by the director of the local administration office. Prior to the process of data collection, the written information about the research project was delivered to the participants along with verbal information. After they agreed to take part in the study, a written informed consent form was contributed to each participant for their signature. All participants were given a small gift as a token of appreciation for their participation after finishing the interview.

RESULTS

A) Characteristics of parents

There were 1,022 participants from 109 DCCs suitable for the analysis. 37.2% were from Chiang Rai, 33.9% were from Phayao and 29.0% were from Chiang Rai. 77.3% were female, the average age was 33.9 years old (SD=10.9, min=17, max=75), 85.3% were married, 92.2% were Buddhist, 36.2% had educational attainment at primary school level, and 30.4 % made 5,001-10,000 baht a month. 46.5% of the mothers were the major care giver, and 49.9% of the participants had 1-3 members in their household.

Case group: 12.1% had a low level of knowledge, 48.0 % had a neutral attitude, and 96.2% had good practice for HFMD prevention and control.

Control group: 38.5% had a high level of knowledge, 52.0% had a positive attitude, and 96.9% had good practice on HFMD prevention and control.

Simple logistic model revealed that there were three factors associated with HFMD. Firstly, the children whose parents were Buddhist had a 1.96 times greater chance of infection than those with Christian parents (90%CI=1.23-3.18). Next, the children whose parents earned bachelor's degree had a 2.29 times greater chance of infection than those with illiterate parents (90%CI=1.23-4.27). Lastly, the children whose parents had a high level of knowledge on HFMD prevention and control had a 1.81 times greater chance of infection than those whose parents had low level of knowledge (90%CI=1.28-2.57) and 2.01 times greater than those whose parents had neutral knowledge (90%CI=1.42-2.85) (Table 1).

B) Characteristic of children

54.9% were male, 56.9% were 3-4 years old, 50.4% were underweight, 15.4% had been admitted to the hospital, and 21.1% had been breastfed for less than 6 months since their birth.

Case group: 55.3% were aged less than 2 years old (mean=2.94, SD=1.02), 57.0% were male, 48.3% were underweight, 18.1% had been admitted to the hospital, 5.6% had a medical condition, and 26.0% had been breastfed for less than 6 months.

Control group: 62.8% were aged 3-4 years (mean=2.94, SD=1.02), 53.7% were male, 51.7% were underweight, 14.1% had been admitted to the hospital, and 81.1% had been breastfed for less than 6 months.

Simple logistic regression model revealed the

TABLE 1. Parents' characteristic and HFMD in a simple logistic regression (1,022).

Characteristics	Total n (%)	Case n (%)	Control n (%)	OR	90%CI	P-value
Total	1022(100.0)	322 (32.4)	690(67.6)	NA		
Sex						
Male	224 (22.7)	73 (22.9)	151 (22.6)	1.00		
Female	762 (77.3)	246 (77.1)	516 (77.4)	1.01	0.77 – 1.39	0.931
Parent's age (years)						
<19	20 (2.2)	4 (1.3)	16 (2.6)	1.00		
20-59	847 (92.7)	288 (93.8)	559 (92.1)	2.06	0.82 – 5.21	0.200
>60	47 (5.1)	15 (4.9)	32 (5.3)	1.87	0.65 – 5.38	0.326
Marital status						
Single	54 (5.4)	16 (5.0)	38 (5.6)	1.00		
Married	854 (85.3)	272 (84.5)	582 (85.7)	1.11	0.67 – 1.84	0.734
Divorce	93 (9.3)	34 (10.6)	59 (8.7)	1.37	0.75 – 2.50	0.393
Family member (person)						
1-3	220 (49.9)	120 (30.4)	210 (36.1)	0.77	0.59 – 1.01	0.068
≥ 4	692 (50.1)	212 (69.6)	480 (63.9)	1.00		
Number of child <12 years in family (persons)						
1	564 (56.7)	206 (63.4)	358 (35.5)	1.00		
2-3	404 (40.6)	111 (34.2)	293 (43.8)	0.65	0.52 – 0.83	0.003*
> 3	28 (2.6)	8 (2.5)	18 (2.7)	0.72	0.38 – 1.58	0.552
Religion						
Buddhist	933 (92.2)	312 (95.1)	621 (90.8)	1.98	1.23 – 3.18	0.018*
Christian	79 (7.8)	16 (4.9)	63 (9.2)	1.00		
Occupation						
Unemployed	72 (7.2)	29 (9.0)	43 (6.4)	1.00		
Merchant	416 (41.6)	140 (43.5)	276 (40.8)	0.75	0.49 – 1.16	0.276
Government Officer	42 (4.2)	21 (6.5)	21 (3.1)	1.48	0.78 – 2.82	0.314
Farmer	324 (32.4)	83 (25.8)	241 (35.6)	0.51	0.33 – 0.80	0.013
Employee	114 (11.4)	39 (12.1)	75 (11.1)	0.77	0.46 – 1.29	0.403
Other	31 (3.1)	10 (3.1)	21 (3.1)	0.71	0.34 – 1.49	0.442
Income (baht/month)						
≤ 5,000	258 (29.3)	87 (29.4)	171 (29.2)	1.09	0.77 – 1.53	0.681
5,001–10,000	303 (30.4)	111 (37.5)	192 (32.8)	1.24	0.89 – 1.72	0.287
10,001–15,000	101 (11.5)	27 (9.1)	74 (12.6)	0.78	0.50 – 1.23	0.371
15,001–20,000	40 (4.5)	14 (4.7)	26 (4.4)	1.52	0.63 – 2.11	0.700
≥ 20,001	179 (20.3)	57 (19.3)	122 (20.9)	1.00		
Education						
Illiterate	48 (4.8)	12 (3.7)	36 (5.3)	1.00		
Primary school	365 (36.2)	125 (38.2)	240 (35.3)	1.56	0.88 – 2.78	0.204
Lower secondary	193 (19.2)	154 (16.5)	139 (20.4)	1.16	0.63 – 2.14	0.679
Higher secondary	236 (23.4)	68 (20.8)	168 (24.7)	1.21	0.67 – 2.20	0.593
Vocational	38 (3.8)	13 (4.0)	25 (3.7)	1.56	0.71 – 3.42	0.352
Bachelor	127 (12.6)	55 (16.8)	72 (10.6)	2.29	1.23 – 4.27	0.028*
Care giver						
Father	92 (9.3)	21 (6.4)	71 (10.7)	1.00		
Mother	462 (46.5)	151 (46.2)	311 (46.8)	1.64	1.06 – 2.55	0.064
Father and Mother	105 (10.6)	35 (10.7)	70 (10.5)	1.69	0.99 – 2.88	0.104
Relatives	333 (33.6)	120 (36.7)	213 (32.0)	1.90	1.21 – 2.99	0.018
Knowledge						
Low (0-6)	172 (17.9)	38 (12.1)	134 (20.7)	1.00		
Medium (7-8)	398 (41.4)	135 (42.9)	263 (40.7)	2.01	1.42 – 2.85	0.001*
High (9-10)	391 (40.7)	142 (45.1)	249 (38.5)	1.81	1.28 – 2.57	0.005*
Attitude						
Neutral (1-3)	476 (49.3)	161 (51.9)	315 (48.0)	1.00		
Positive (4-5)	490 (50.7)	149 (48.1)	341 (52.0)	0.86	0.68 – 1.07	0.256
Practice						
Neutral (1-3)	32 (3.3)	12 (3.8)	20 (3.1)	1.00		
Good (4-5)	936 (96.7)	301 (96.2)	635 (96.9)	0.79	0.43 – 1.46	0.526

*Significant level at α=0.10

TABLE 2. Children characteristic and HFMD in simple logistic regression.

Characteristics	Total n (%)	Case n (%)	Control n (%)	OR	90%CI	P-value
Age						
≤ 2	325 (34.2)	147 (55.3)	178 (26.0)	7.94	4.20-15.04	<0.001*
3-4	541 (56.9)	111 (41.7)	430 (62.8)	2.48	1.32-4.69	0.019*
>4	85 (8.9)	8 (3.0)	77 (11.2)	1.00		
Sex						
Male	403 (54.9)	150 (57.0)	253 (53.7)	1.00		
Female	331 (45.1)	113 (43.0)	218 (46.3)	0.87	0.68-1.13	0.386
BMI						
Underweight	234 (50.4)	83 (48.3)	151 (51.7)	1.29	0.73-2.29	0.455
Normal	183 (39.4)	75 (43.6)	108 (37.0)	1.63	0.92-2.92	0.162
Overweight	47 (10.1)	14 (8.1)	33 (11.3)	1.00		
History of hospital admission						
Yes	151(15.4)	57 (18.1)	94 (14.1)	1.34	0.99-1.82	0.110
No	829(84.6)	258 (81.9)	571 (85.9)	1.00		
Medical condition						
Yes	53 (5.3)	18 (5.6)	35 (5.2)	1.00		
No	938 (94.7)	302 (94.4)	636 (94.8)	0.92	0.56-1.50	0.789
Breast feeding (month)						
< 6	145 (21.1)	55 (26.0)	90 (18.9)	1.52	1.10-2.10	0.031*
≥ 6	542 (78.9)	155 (73.8)	387 (81.1)	1.00		

* Significant level at α=0.10

TABLE 3. Factors associated with HFMD in multiple logistic regression.

Factors	OR	95%CI	P-value
Age (year)			
≤ 2	7.05	3.25 – 15.28	<0.001*
3-4	2.09	0.97 – 4.51	0.061
>5	1.00		
Family member (person)			
1-3	1.43	1.04 – 1.97	0.028*
≥ 4	1.00		
Knowledge			
Low (0-6)	1.00		
Medium (7-8)	2.35	1.47 – 3.77	<0.001*
High (9-10)	1.61	1.00 – 2.59	0.051

* Significant level at α=0.05

factors significantly associated with HFMD. Firstly, the children aged ≤ 2 years had a 7.94 times greater chance of acquiring HFMD than those aged more than 4 years (90%CI=4.20-15.04) and 2.48 times greater than those aged 3-4 years (90%CI=1.32-4.69). Besides, the children who had been breastfed for less than 6 months had a 1.52 times greater chance to having HFMD than those who had been breastfeed for 6 months or more (90%CI=1.10-2.10).

After all possible factors were controlled; it was found that three factors were associated with HFMD in the children. The children aged ≤ 2 years old had a 7.05 times greater chance of HFMD infection than those children aged more than 5 years old (95%CI=3.25-15.28). Furthermore, the children from the family with 1-3 members had a 1.43 times greater chance of acquiring HFMD than those from the family with ≤ 4 members.

DISCUSSION

The results from the simple model showed that the children whose parents were Buddhist had a 1.98 times greater chance of having HFMD than those with Christian parents; however, the significance was not found in the multiple model. HFMD might not be directly connected to religions, but some rural areas of Thailand have had a quicker economic growth.[22] The economic growth makes the parents from those rural areas, where one religion might be predominate than others leave their children at a day care center so they can go to work. Day care centers organized by the local government take care of preschool children during daytime. However, there was no previous report on the association between religions and HFMD.

In this study, the children aged ≤ 2 years old had a 7.05 times greater chance of HFMD infection than those aged more than 5 years old. According to the report of HFMD assessment in Thailand, the age group with high morbidity was mainly the children aged 0-2 years old who were immunosuppressed.[5] This is also consistent with Liu's study.[23] In Taiwan, it was found that patients with HFMD were often children aged less than 3 years old, similarly in Vietnam and China, the occurrences of HFMD were found in children younger than 3 years old. Another study by Chan et al.[24] also found that most patients were the children aged from 1 to 2.9 years old. In terms of household members, the households with 1-3 members had a 1.43 times greater chance of HFMD infection than those with ≥ 4 members. It could be that the current population characteristic of Northern Thailand is mostly a single family with few members as most families in the rural areas often have only 1-2 children. The number of family members may contribute to the prevention of HFMD due to the number of members who had to keep clean. The results of this study support the study of YIN and et al.[25] indicating that families with children who had a history of HFMD infection was one of the factors contributing to HFMD.

Regarding the knowledge of HFMD, the parents with moderate level of knowledge had a 2.36 times greater chance of HFMD infection in their children than those with low level of knowledge. This study had been conducted to investigate HFMD infection since the past few years. After that, these groups of parents had more experience in children's care and learned more about HFMD. However, knowledge is important because the correct knowledge leads to appropriate practice in HFMD prevention and control.[16,26]

Generally parents or care givers at home with knowledge, good attitude and good practices of personal and environmental hygiene should have children who are less susceptible to HFMD. It is necessary to find out why children whose parents had moderate knowledge of HFMD turn to have a higher chance of contracting HFMD. May be having knowledge alone is not enough and parent and care givers at home, need knowledge of good practice and preventive measures of HFMD.[4]

Day care center is the place that often found and report HFMD cases as it is a crowded place where a lot of children are living together[11] and the children are usually under 5 years old with low immune system and lack of personal healthcare.[22] Moreover, care givers with deficient knowledge might misunderstand how to prevent and control HFMD.[27] Although the Ministry of Public Health has released the annual health measure for HFMD control in children's care centers, there are still HFMD outbreaks every year. Although this study did not focus on care givers at DCC, it is clear from other reports, that care givers are very crucial in the prevention and control of HFMD, since they spend more time during the day with a lot of children in a crowded place. Their knowledge and practices of safe and simple personal and environmental hygiene is vital to the prevention and control of HFMD[2] in their study of the knowledge and practice in prevention control of HFMD stated that, care givers at DCC have enough knowledge of HFMD but their knowledge of prevention of HFMD is not enough and simple practices such as screening of children at the entrance of the DCC before admission every morning may be the most efficient method of prevention of HFMD. Further studies may be needed in the HFMD preventive practices knowledge of care givers.[3]

There are several factors influencing HFMD such as the parents being Buddhist, the duration of breastfeeding, the parents' knowledge on prevention and control of HFMD, and importantly, how to keep day care center's environment clean. Interestingly, HFMD prevention in day care centers involves indoor and outdoor environment conditions of the centers, for instance, cleaning the contaminated surfaces with effective disinfection agent.[26] Another interesting issue is the guideline for HFMD prevention and control. Even though Thailand had issued the measure of HFMD prevention and control in day care centers, outbreaks are still present. Thus, it is essential to develop a proper guideline for HFMD prevention and control which can effectively and practicably help control the disease. It is obvious that whichever measures are adopted, care givers both at home and at DCC should be educated and well informed of the useful preventive measures to support each other in the prevention and control of HFMD.[4]

CONCLUSION

This study found that the factors including children aged less than 2 years old, 2-3 family members per household, and parents' knowledge of HFMD prevention and control are related to HFMD in upper Northern Thailand. Therefore, Thailand should concentrate on children at an early age with low immunity and the number of members in each family and promote the importance of knowledge and understanding of HFMD prevention and control among parents and care givers because these all play crucial roles in HFMD prevention and control.

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Associated Factors of Subtherapeutic Serum Magnesium Level for Prevention of Eclampsia in Term Pregnant Women with Severe Pre-eclampsia

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ABSTRACT

Objective: To investigate the factors associated with subtherapeutic serum magnesium levels in order to prevent eclampsia in term pregnant women with severe pre-eclampsia.

Methods: This case-control study included 200 term pregnant women with severe pre-eclampsia who received magnesium sulfate for eclampsia prophylaxis. These patients were randomly allocated into case and control groups. Experimental cases included 100 women whose serum magnesium level did not reach the therapeutic level (<4.8 mg/dL) at 2 hours after initial administration, whereas the controls were 100 women whose serum magnesium levels reached therapeutic levels (4.8-8.4 mg/dL). Data from the medical records, including baseline characteristics, sign and symptoms, laboratory findings and pregnancy outcomes, were extracted for univariate and multivariate analyses.

Results: Only two factors, pre-pregnancy body mass index (BMI) and serum creatinine level, showed significant differences between the two groups. Pre-pregnancy BMI greater than 25 kg/m^2 increased the risk of subtherapeutic serum magnesium level by 56% compared with normal pre-pregnancy BMI (adjusted OR 1.56, p=0.019), whereas pre-pregnancy BMI less than 18 kg/m^2 decreased the risk by 80% (adjusted OR 0.2, p=0.02). Also, serum creatinine levels greater than 0.9 mg/dl decreased the risk by 98.7% (adjusted OR 0.013, p<0.001). No significant difference in pregnancy outcomes was noted in either group.

Conclusion: Pre-pregnancy BMI greater than 25 kg/m^2 increased the risk, whereas pre-pregnancy BMI less than 18 kg/m^2 decreased the risk of subtherapeutic serum magnesium levels. A serum creatinine level greater than 0.9 mg/dl was another factor that decreased the risk.

Keywords: Pre-eclampsia; magnesium sulfate; therapeutic level; associated factors (Siriraj Med J 2020; 72: 159-166)

INTRODUCTION

Pre-eclampsia is a common obstetric complication and one of the main causes of maternal and fetal mortality worldwide1. The incidence of pre-eclampsia varies between 3-10 percent of pregnant women and is the leading cause of maternal deaths. The causes of such deaths include intracerebral hemorrhage, congestive heart failure, acute kidney injury, and eclampsia.[1] Maternal complications and neonatal complications, such as preterm labor and respiratory distress syndrome, are also common.

Given that the etiology of eclampsia is unknown, but the condition occurs exclusively during pregnancy, the best treatment of choice is termination of pregnancy.[2] However, other supportive treatments, including prevention of eclampsia, blood pressure control and patient hydration, should also be considered.[2-4]

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For prevention of eclampsia, magnesium sulfate is the most appropriate treatment of choice.[5] There are two major regimens that are currently used.

1. Zuspan regimen: an intravenous regimen of 4 grams of magnesium sulfate is administered as the loading dose, followed by a maintenance infusion of magnesium sulfate solution at 2 grams/hour.[6]
2. Pritchard regimen: an intramuscular regimen of 4 grams of magnesium sulfate is administered as the loading dose, followed by 10 grams intramuscularly. Subsequently, 5 grams is administered intramuscularly every 4 hours in alternate buttocks.[7]

At Siriraj Hospital, we use the intravenous regimen because it can be easily adjusted to reach the target therapeutic level.[8]

Surprisingly, even subtherapeutic serum magnesium levels might cause serious maternal complications such as intracerebral hemorrhage and multiple organ failure. However, only one study by Tudela CM[9] reported the factors associated with subtherapeutic serum magnesium levels for the prevention of eclampsia in pre-eclamptic pregnant women. This study reported subtherapeutic serum magnesium levels in more than half of the participants. In addition, various factors associated with this condition, including body mass index (BMI), age and multipara, were reported.

Until now, no such study has been conducted in Thailand. We seek to determine the factors associated with subtherapeutic serum magnesium levels and whether these factors differ between our country and the Western countries.

The primary aim of this study was to identify the factors associated with subtherapeutic serum magnesium levels for the prevention of eclampsia in term pregnant women with severe pre-eclampsia. The secondary aim was to compare the pregnancy outcomes, including delivery outcomes, maternal outcomes and neonatal outcomes, as well as the use of antihypertensive drugs in these pregnant women.

MATERIALS AND METHODS

Study design

This was a case-control study with a retrospective chart review.

Sample size calculation

The test of difference between two independent proportions was chosen to calculate the sample size in this study, based on the study of Tudela CM[9] that reported associated factors related with subtherapeutic serum magnesium level in pre-eclampsia pregnant women. From this study, obesity (BMI >25 kg/m^2) and multipara were two factors that were strongly related to subtherapeutic serum magnesium levels. Obese and multipara pregnant women accounted for 83% and 59%, respectively, of the 2,698 women in the subtherapeutic serum magnesium level group and approximately 54% and 41%, respectively, of the 2,600 women in the therapeutic serum magnesium level group.

Given that multipara was the factor which accounted for a small percentage, we chose it as the factor for calculation of sample size. Using this factor for the calculations, the sample size would be sufficiently large to identify a significant difference in our study.

After calculation, 200 participants, i.e., 100 participants in each group were required for this study.

Intervention

After approval by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si 580/2014), all medical records of term pregnant women with severe pre-eclampsia who delivered their babies in Siriraj Hospital from January 2006 to December 2013 were reviewed and extracted for further study. The exclusion criterion included pregnant women who developed eclampsia before magnesium sulfate administration.

Two hundred medical records that met the inclusion criteria were randomly allocated into two groups as follows:

1. Case group: 100 pregnant women with subtherapeutic serum magnesium levels (<4.8 mg/dl).
2. Control group: 100 pregnant women with therapeutic serum magnesium levels (4.8-8.4 mg/dl).

Measurement of serum magnesium level in Siriraj Hospital

Serum magnesium levels were assessed using the standard Roche/Hitachi Cobas c systems.[10-12]

All the basic characteristics, signs and symptoms of pre-eclampsia, laboratory findings, antihypertensive drug use and pregnancy outcomes were carefully extracted from the patients' medical records and compared between the case and control groups.

Statistical analysis

Quantitative data, such as age, pre-pregnancy BMI, and total weight gain, were analyzed with the help of a two-sample t-test.

Qualitative data, such as pregnancy outcomes and antihypertensive drug use, were analyzed using the Chi-square test.

A logistic regression model was used for the multivariate analysis. The outcomes were quantified as percentage and odds ratio with a 95% confidence interval. A P-value < 0.05 was considered significant. All analyses were performed with the SPSS version 20 statistical package.

RESULTS

We started with univariate analysis to compare the basic characteristics between the case and control groups. The case group had a significantly higher number of pregnant women with a pre-pregnancy BMI greater than 25 kg/m^2 than the control group, whereas the number of pregnant women with a pre-pregnancy BMI less than 18 kg/m^2 was lower in the case group than in the control group. All the findings are presented in Table 1.

The laboratory results, including the renal function test (creatinine, uric acid), the liver function test (AST, LDH) and hematology (platelet), exhibited significant differences between groups. The details are provided in Table 2.

All of the signs and symptoms of pre-eclampsia, including headache, blurred vision, epigastric pain, leg edema and pulmonary edema, were not significantly different as shown in Table 3.

TABLE 1. Basic characteristics of the subjects.

	Subtherapeutic level n*=100	Therapeutic level n*=100	*P*-value
Age (year)	28.24 ± 6.36#	28.64 ± 6.61#	0.633
Prepregnancy BMI (kg/m^2)			
<18.5	6 (6%)	32 (32%)	<0.001
18.5-24.9	55 (55%)	61 (61%)	
≥25	39 (39%)	7 (7%)	
Total weight gain (kg)			<0.001
Underweight gain	23 (23%)	37 (37%)	
Normal weight gain	19 (19%)	41 (41%)	
Overweight gain	58 (58%)	22 (22%)	
Nullipara	59 (59%)	69 (69%)	0.226
Associated condition and diseases			
DM			0.688
GDMA1	10 (10%)	8 (8%)	
GDMA2	3 (3%)	1 (1%)	
Overt DM	3 (3%)	2 (2%)	
Chronic HT	19 (19%)	10 (10%)	0.071
Other	7 (7%)	8 (8%)	0.788
Smoking	2 (2%)	2 (2%)	1.00
Alcohol	3 (3%)	1 (1%)	0.621
Drug abuse	3 (3%)	1 (1%)	0.621

*n = number, Data was presented as Mean ± SD or n (%)

TABLE 2. Laboratory findings.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Renal function test			
Creatinine (mg/dl) >0.9	6 (6%)	81 (81%)	< 0.001
Uric acid (mg/dl) >8	7 (7%)	36 (36%)	< 0.001
Hematology			
Platelet (x10^3/µl) < 100,000	1 (1%)	4 (4%)	0.001
Liver function test			
AST (U/L) >70	1 (1%)	9 (9%)	0.009
ALT (U/L) >70	1 (1%)	6 (6%)	0.059
LDH (U/L) >600	5 (5%)	17 (17%)	0.006

*n = number

TABLE 3. Signs and symptoms of preeclampsia.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Headache	10 (10%)	17 (17%)	0.147
Blur vision	9 (9%)	7 (7%)	0.602
Epigastric pain	8 (8%)	8 (8%)	1.00
Leg edema	61 (61%)	52 (52%)	0.199
Pulmonary edema	1 (1)	0 (0)	1.000

*n = number

The number of pregnant women who used antihypertensive drugs was significantly increased in the case group compared with the control group. The details of antihypertensive drug use are reported in Table 4. Overall pregnancy outcome exhibited no significant differences for any of the variables as shown in Table 5. After the univariate analysis was performed, the multivariate analysis was performed to eliminate the confounding factors by reanalyzing all of the significant factors associated with subtherapeutic serum magnesium levels. The odds ratio was used for the prediction of subtherapeutic magnesium levels. The multivariate analysis results identified two factors that exhibited a significant association with subtherapeutic serum magnesium levels, which included pre-pregnancy BMI and serum creatinine levels. Pregnant women with a pre-pregnancy BMI greater than 25 kg/m^2 exhibited a 56% increased risk of having subtherapeutic levels compared with women with a normal pre-pregnancy BMI (18-24.9 kg/m^2). In contrast, pregnant women with a pre-pregnancy BMI less than 18 kg/m^2 exhibited an 80% decreased risk. In addition, serum creatinine levels greater than 0.9 mg/dl also decreased the risk of subtherapeutic serum magnesium levels by 98.7%. The details of the multivariate analysis are presented in Table 6.

TABLE 4. Antihypertensive drug use after magnesium administration.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Amlodipine	1 (1%)	0 (0%)	
Hydralazine	18 (18%)	14 (14%)	
Labetalol	20 (20%)	6 (6%)	
Total	39 (39%)	20 (20%)	0.003

*n = number

TABLE 5. Pregnancy outcomes.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Delivery outcome			
Spontaneous vertex delivery	28 (28%)	37 (37%)	0.235
Vacuum extraction	7 (7%)	10 (10%)	
Forceps extraction	0 (0%)	1 (1%)	
Cesarean section	64 (64%)	52 (52%)	
Others	1 (1%)	0 (0%)	
Maternal outcomes			
Eclampsia	0 (0%)	0 (0%)	-
Post-partum hemorrhage	3 (3%)	5 (5%)	0.498
Intracerebral hemorrhage	0 (0%)	1 (1%)	0.497
Sepsis	1 (1%)	1 (1%)	1.000
Intensive unit care admission	0 (0%)	2 (2%)	0.246
Blood transfusion	1 (1%)	3 (3%)	0.369
Death	0 (0%)	0 (0%)	-
Neonatal outcomes			
Apgar score <7			
At 1 minute	7 (7%)	9 (9%)	0.431
At 5 minutes	4 (4%)	1 (1%)	0.184

*n = number

TABLE 6. Multivariate analysis of associated factors of subtherapeutic serum magnesium level.

	Adjusted OR (95% CI)	*P*-value
BMI (kg/m^2)		0.002
< 18	0.20 (0.05,0.77)	0.020
18-24.9	1.00	
≥ 25	1.56 (1.32,23.41)	0.019
Weight gain (kg)		0.066
Under weight gain	0.79 (0.23,2.77)	0.720
Normal weight gain	1.00	
Over weight gain	2.92 (0.88,9.75)	0.081
Creatinine (mg/dl)		<0.001
≤ 0.9	1.00	
> 0.9	0.013 (0.004,0.047)	
Uric acid (mg/dl)		0.616
≤ 8	1.00	
> 8	1.45 (0.34,6.08)	
Platelet count (µl)		0.247
≥ 100,000	1.00	
< 100,000	0.21 (0.01,2.92)	
AST (U/L)		0.958
≤ 70	1.00	
> 70	1.07 (0.08,14.54)	
LDH (U/L)		0.091
≤ 600	1.00	
> 600	0.24 (0.05,1.26)	

DISCUSSION

The association of subtherapeutic serum magnesium levels with the prevention of eclampsia in pre-eclamptic pregnant women was first proposed by Tudela CM.[9] In that study, more than half of the participants exhibited subtherapeutic serum magnesium levels. That study also reported factors associated with subtherapeutic serum magnesium levels in pre-eclamptic pregnant women, including BMI, age and multipara status.

According to our multivariate analysis, the only two factors that exhibited significant association with subtherapeutic serum magnesium levels were pre-pregnancy BMI and serum creatinine level.

Similar to the study of Tudela CM.[9], the outcome of pre-pregnancy BMI indicated that pregnant women with a BMI greater than 25 kg/m^2 exhibited a 56% increased risk of subtherapeutic serum magnesium levels compared with pregnant women with a normal BMI (18-24.9 kg/m^2).

In addition, those with a BMI less than 18 kg/m^2 exhibited an 80% decreased risk of subtherapeutic serum magnesium levels.

Based on the magnesium metabolism theory, the constant proportions of magnesium distribution in the human body under normal conditions are as follows: soft tissue, 19.3%; muscle, 27%; bone, 52.9%; serum, 0.3%; and red blood cell, 0.5%. Obese women have more fat, bone and muscle mass than women with normal BMI, potentially explaining the relationship of BMI and serum magnesium levels. Pregnant women with increased BMI exhibit an increased distribution of magnesium to fat, bones and muscle, which would reduce the magnesium distribution in the serum. In addition, women with an increased BMI had more blood volume, which might dilute the serum magnesium level. Based on this mechanism, women with increased BMI have a tendency to have subtherapeutic serum magnesium levels.[13-16]

The kidneys are the crucial organs for controlling magnesium homeostasis. A serum creatinine level greater than 0.9 mg/dl reflects the reduced efficacy of the kidney in magnesium excretion. This physiology supported our finding that the subtherapeutic serum magnesium level decreases the risk by up to 98.7%.

The number of pregnant women who needed antihypertension drugs in our study increased in the subtherapeutic serum magnesium level group compared with the therapeutic serum magnesium level group. The finding can be explained by the effect of magnesium sulfate, which can also decrease the blood pressure by modulating vascular tone. Therefore, the pregnant women with lower serum magnesium levels in the subtherapeutic group might require more antihypertensive drugs.

With regard to the comparison of pregnancy outcomes, there were no statistically significant differences in terms of delivery outcomes, maternal outcomes and neonatal outcomes in either group. The explanation for these findings is that not only the serum magnesium level, but also many other confounding factors can influence the outcomes.

The use of a case-control study design for this study is useful for determining the significant outcomes for multiple risk factors. The criteria for selecting subjects were carefully considered to control the heterogeneity and selection bias affecting the similarity of the basic characteristics of both groups.

At Siriraj Hospital, we manage pregnant women with severe pre-eclampsia according to our institutional guidelines. The same practice of history taking, physical examination, and laboratory investigation and the same protocol for intravenous regimens of magnesium sulfate were used for each patient. Therefore, most of the retrospective data were completely recorded, and the minimal deviation of data collection increased the reliability of this study.

However, the retrospective nature of the study presented some limitations. Patient data from our medical records were documented by many physicians. Many subjective data, such as the signs and symptoms of pre-eclampsia, may vary.

This study found that the factors associated with subtherapeutic serum magnesium levels included pre-pregnancy BMI and serum creatinine levels. This result could be applied to daily medical practice by increasing the dosage of magnesium sulfate in pregnant women of the subtherapeutic serum magnesium level group, including women with a pre-pregnancy BMI greater than 25 kg/m^2. In addition, physicians should be cautious when administering magnesium sulfate to those with a pre-pregnancy BMI less than 18 kg/m^2 or those with greater than 0.9 mg/dl serum creatinine.

However, because there are only a few studies available on this subject, further studies should be performed, especially prospective studies, and a risk scoring model for subtherapeutic serum magnesium levels should be developed. We hope that the future guidelines for the management of pre-eclamptic women will include more evidence-based data, which in turn can improve the outcomes of management for these patients.

CONCLUSION

The factors associated with subtherapeutic serum magnesium levels were pre-pregnancy BMI and serum creatinine levels. A pre-pregnancy BMI greater than 25 kg/m^2 increased the risk of subtherapeutic serum magnesium levels in severe pre-eclamptic women, whereas pre-pregnancy BMI less than 18 kg/m^2 decreased the risk. Serum creatinine levels greater than 0.9 mg/dl also decreased the risk of subtherapeutic magnesium levels in these women.

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Increase in Endothelin-1 Expression in Umbilical Cord Arteries in Preeclampsia

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ABSTRACT

Objective: Endothelin1 (ET1) is 21- amino acid vasoconstrictor peptide secreted by endotheliumwhich has an important role in the pathoohysiology of preeclampsia (PE). The objective of this study was to evaluate the binding sites and quantitative changes in ET1 in umbilical cord vessels of PE patients.

Methods: This study recruited 40 pregnant women between 20-40 years old at 3rd trimester. All cases selected for this study underwent an elective cesarean section, grouped into 2 groups; PE group of 20 pregnant women (at 3rd trimester) who proved to have pregnancy induced hypertension and proteinuria. The control group was of 20 healthy pregnant females at the same average of gestational age and with the same exclusion criteria and no PE, underwent elective caesarean section. Umbilical cord tissues were taken from the maternal side, fixed with formalin, paraffin, embedded sections of umbilical cord were treated with Endothelin1 antibody. The immunoreactivity of ET1 was assessed using Aperio image scope software. Statistical analysis was done using SPSS program.

Results: The results demonstrated a significant increase (P = 0.001) of ET1 expression in cord vessels of PE group with respect to control group (mean 28.5±1.7, 2.6±0.4 respectively).

Conclusion: It is concluded that ET1 is markedly increase in PE and may be the cause behind promoted vascular smooth muscle cell contraction and blood pressure elevation in PE.

Keywords: Endothelin1; preeclampsia; pregnancy; umbilical cord (Siriraj Med J 2020; 72: 167-173)

INTRODUCTION

The umbilical cord is the fundamental connection between developing fetus and the placenta. It is made of three blood vessels; two small arteries, which carry the deoxygenated blood from the fetus to the placenta and a one large vein which carries nutrition-rich oxygenated blood to the fetus; this vein is unlike the regular veins in that it contains a layer of smooth muscles.[1] These blood vessels lie in an embryonic gelatinous connective tissue known as Wharton's jelly, all are enclosed in a layer of amnion.[2] The blood vessels of human umbilical cord are dissimilar from the main vessels of the same caliber in the body for many reasons; exudation of fluid take place in these vessels and participate to the formation of the

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amniotic fluid.[3] Umbilical vessels lack vasa vasorum, thus rely on their own oxygen supply, making them more vulnerable to modification in hemodynamic status.[4]

Hypertension is a commonly occurs during pregnancy. Preeclampsia (PE) is disorder that occurs in pregnancy that damages both the mother's circulation and the fetal growth. The risk factors for development of PE includes obesity, insulin resistance and hyperlipidemia all these conditions will lead to increase in the release of inflammatory mediators and rise the oxidative stress which will eventually lead to dysfunction of the endothelium.[5] PE occurs at 20 weeks gestation and onward, it is characterized by an elevation in blood pressure higher than "140/90 mm Hg" accompanied by significant proteinuria " ≥300 mg/dl in 24-hour urine collection".[6] PE affects many pregnancies and is still considered as a dangerous risk to mother and fetus.[7,8] PE is much higher in association with intrauterine growth retardation because there might be a chronic hypoxia which leads to contraction of the placental vascular bed which eventually increases the arterial resistance.[4,8]

Endothelins are family of 21-amino acid peptides encoded by 3 genes and produced in several tissues, mainly by endothelial cells lining blood vessels; they are group of vasoconstrictor peptides covering three isoforms, endothelin-1, endothelin-2, and endothelin-3. "ET1, ET2, and ET3" characterize by the presence of 2 intramolecular disulfide bonds.[9] ET1 is the main isoform made by vascular endothelium. Once formed, ET1 acts as a paracrine and autocrine mediator rather than an endocrine hormone, it has strong vasoactive performance and has been involved in the pathogenesis of a lot of vascular diseases like hypertension,[10] which can cause fibrosis of blood vessels and a state of inflammation due to increase in cytokine production.[11] When ET1 is released by the endothelium, it performs its action on ETA and ETB receptors of the neighboring endothelium or smooth muscle cells by paracrine or autocrine manner. The genes for ETA and ETB receptors had been cloned. ETA and ETB receptors on smooth muscle induce many cellular activities such as contraction, proliferation cell hypertrophy and apoptosis,[12] studies in animal models representative of PE, have shown that endothelin receptor blockers prevent the development of this disease.[13] Large quantity of Endothelin-1 was demonstrated in human umbilical vessels, amniotic membrane ,amniotic fluid and placenta.[14] This research aims to evaluate the binding sites for Endothelin-1 in the vessels of the umbilical cord and to quantify the differences in expression of Endothelin-1 in these vessels of women with in PE.

MATERIALS AND METHODS

Sample collection

The sample size was determined using Raosoft tool with the confidence level set at 95% and the margin of error is 10% with the resultant sample size required is 20 patients with preeclampsia.

The present study enrolled 40 pregnant women ageing between 20-40 years old at the third trimester who attended AL- Imamayn Al-Khademyiayn medical city hospital in Baghdad who underwent elective cesarean section. The choice of patients undergoing cesarean section was because we wanted to standardize the method of delivery and it is easier to attend to the patient and harvest the fresh placenta immediately upon delivery.

The exclusion criteria are patients with hypertension before pregnancy, diabetes mellitus, vascular diseases and smoking.

The Patients were grouped into two groups of 20. Group I "PE group" consisted of pregnant women (at third trimester) who had systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg and proteinuria of at least 1+ (≥300 mg/dl). Group II "control" consisted of normotensive pregnant women at the same average age (systolic BP <140 mmHg and diastolic BP <90 mmHg). Written consent was obtained from the patients after explaining the procedure to them. The present study was approved by the Head of the Postgraduate Committee, Department of Applied Embryology, High Institute of Infertility Diagnosis and ART, Al-Nahrain University.

Immunohistochemical staining with Endothelin-1 antibody (ET-1)

The placenta and umbilical cord was collected during the caesarean section procedure. Transvers pieces of the umbilical cords "one cm in thickness" was taken from the maternal side (area close to the placenta) of each patient, fixed in 10% buffered formal saline, dehydrated by ascending concentrations of ethanol, cleared in xylene, impregnated and embedded in paraffin wax. Paraffin sections of 4 µm thickness were placed on positively charged slides then the sections incubated overnight at room temperature. The tissue sections were de-paraffinized and rehydrated, blocked with peroxidase and serum blocking reagents, treated with ET-1was purchased from Abcam (a30536) Primary antibody was diluted in a serum block-to (1/100) µg/ml as determined by titration and was added in sufficient volume to cover the tissue.and incubated overnight with biotinylated secondary antibody and HRP-streptavidin complex respectively, then treated with DAB chromogen, stained by haematoxylin as counter stain, dehydrated

by series of ethanol, cleared in xylene and covered with cover slips. The immunoreactivity of ET1 was assessed quantitatively by Aperio Image Scope software. The computerized analysis of the immunohistochemical reactivity of ET1 using Aperio image scope program was done by choosing a determined area from each sample which had no spaces and then enter the picture to the program which read the negative, weak positive, positive and strong positive reaction in the cells. The positive reading included positive and strong positive cells we excluded the weak positive. The accuracy of the reading was ensured by repeating the reading three times and taking the mean.

Statistical analysis

The IBM Corp. SPSS Statistics for Windows, Version 23 Armonk, NY: IBM Corp. was used to analyze the data. All data in this study are presented as mean ± SEM. Data were analyzed by Mann-Whitney U test, the value of $p < 0.05$ was considered as statistically significant.

RESULTS

The umbilical arteries of the control group have constricted, folded shaped endothelium and their wall consist of pale staining layer of variable thickening in the center called 'tunica intima' which is surrounded by muscular layer called 'tunica media'. The medial layer is closely attached to the surrounding Wharton's jelly which is merged with tunica adventitia in umbilical vessels (Fig 1) while in PE group this layer is clearly separated from the jelly due to the presence of strong vasoconstriction which may lead to narrowing the lumen Fig 1.

In the control group, SMCs of arterial wall are fusiform shaped concentrically closely arranged with each other with elongated, large nuclei having wavy like appearance (Fig 2A). While in PE group, the muscle cells are irregularly arranged and the nuclei become small sized losing their longitudinal appearance. Irregular spaces appear between SMCs lead to accumulation of these cells in groups due to increase inter cellular fluid which is associated with edema. The presence of these spaces in the PE cords made it easier to distinguish between the muscle cells than it is in the control group (Fig 2B).

The immunoreactivity for ET1 appeared as small dark brown granules or deposits concomitant with the structural arrangement of the cord when visualized by DAB using the haematoxylin as a counter stain. The reaction mainly occurred in the cytoplasm of smooth muscle fibers and to a lesser extent in the endothelium lining blood vessels (Fig 3A). The strongest staining reactivity pattern was observed in the smooth muscle fibers seen as high intense brownish granules especially in the arteries of PE samples (Fig 3B).

The positivity of the vascular smooth muscle cells varied between strong positive and positive. In spite of the difference in the thickness of vascular smooth muscle layer in between PE group and control group, the number of cells that showed strong positive reaction to ET1 was significantly high (Fig 4A). In contrast, the control samples showed large number of weakly stained smooth muscle cells when treated with ET1 antibody, tunica adventitia showed no reactivity at all (Fig 4B). The expression percentage of ET- 1 was significantly increased in PE patients compared to the control group Fig 5.

DISCUSSION

Several theories have been suggested about the eventual cause of preeclampsia, it is clear that in PE there is an abnormal vascular remodeling.[15] It has been demonstrated that the remodeling of spiral arteries is not complete in these patients.[16] Reduction of utero-placental perfusion as a consequence of anomalous cytotrophoblast invasion of the spiral arterioles is a prompting episode leading to preeclampsia.[17] Ischemia/hypoxia in the placenta is believed to induce abnormal endothelial function leading to the release of vasoactive substances such as "nitric oxide, endothelin, and angiotensin II" that have intense effects on blood flow and arterial pressure regulation.[18,19] Due to the fact that human umbilical cord vessels have a special feature in being deficient of innervation, the action of the vasoactive substances seemed to be decisive in monitoring the tone of the umbilical vessels; several studies have demonstrated that the production of vasoactive substances, such as nitric oxide and ET1 are changed in PE in comparison with normotensive pregnancies.[20,21]

The choice of patients undergoing cesarean section was because we wanted to standardize the method of delivery and it is easier to attend to the patient and harvest the fresh placenta immediately upon delivery. We don't think that the mode of delivery would affect the rate of expression of ET1.

ET-1 is a strong vasoactive peptide, its concentration is increased in PE and plays a serious role in the pathophysiology of PE; there are many investigation on the role of ET1 in the stimulation of hypertension in PE. Indeed, ET1 was observed to prompt vasoconstriction via the ETA receptor, which had been shown to induce hypertension in PE.[22,23] The concentration of ET1 was found to be 3 times higher in the plasma umbilical cord than in

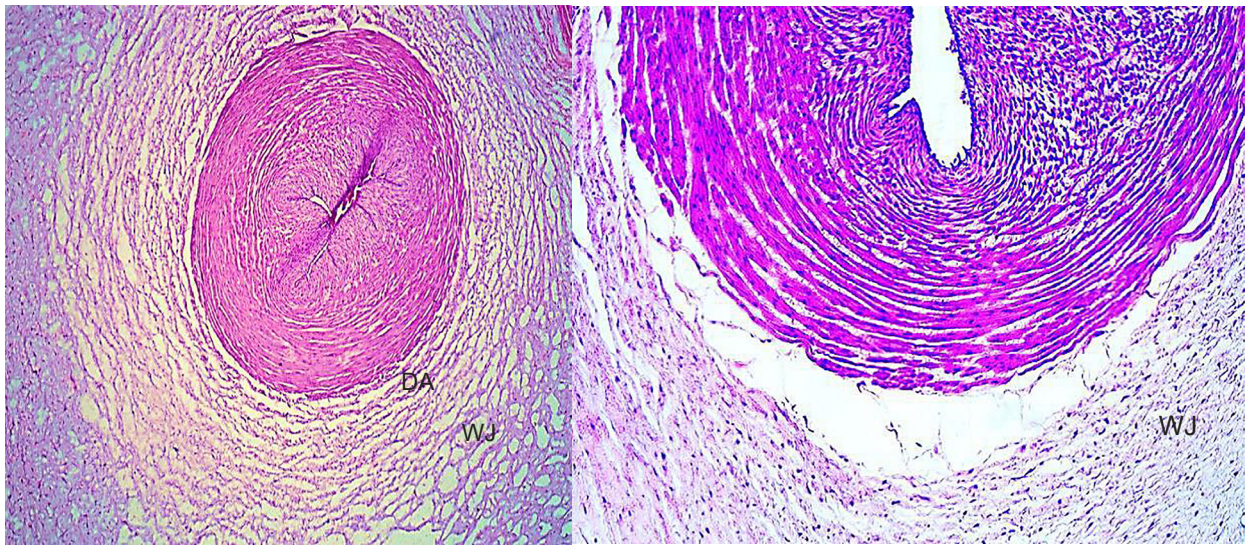

Fig 1. **(A)** Cross section of umbilical cord of control group shows the general appearance of the umbilical artery where its tunica adventitia (AD) merged with Wharton's jelly (WJ) control group, H&E stain, X40. **(B)** Cord in PE group show the separation of the medial layer of umbilical artery from the surrounding Wharton's jelly, H&E, X100.

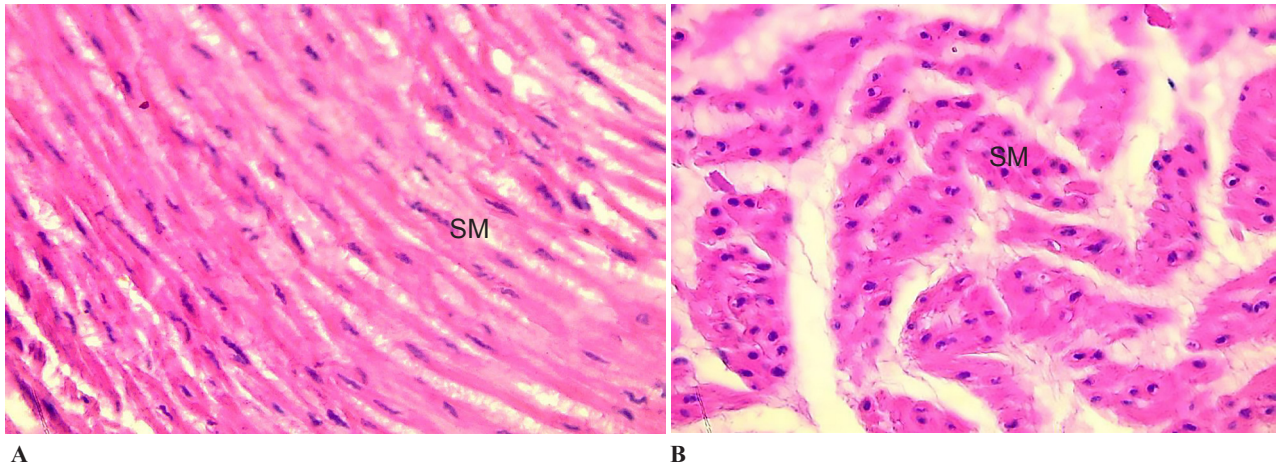

Fig 2. **(A)** Cross section of the umbilical artery shows the normal concentrically arranged smooth muscle (SM) in arterial wall of control group. **(B)** Irregularity of SM with an increase in the inter-cellular spaces between these cells in PE group. H&E stain, X400

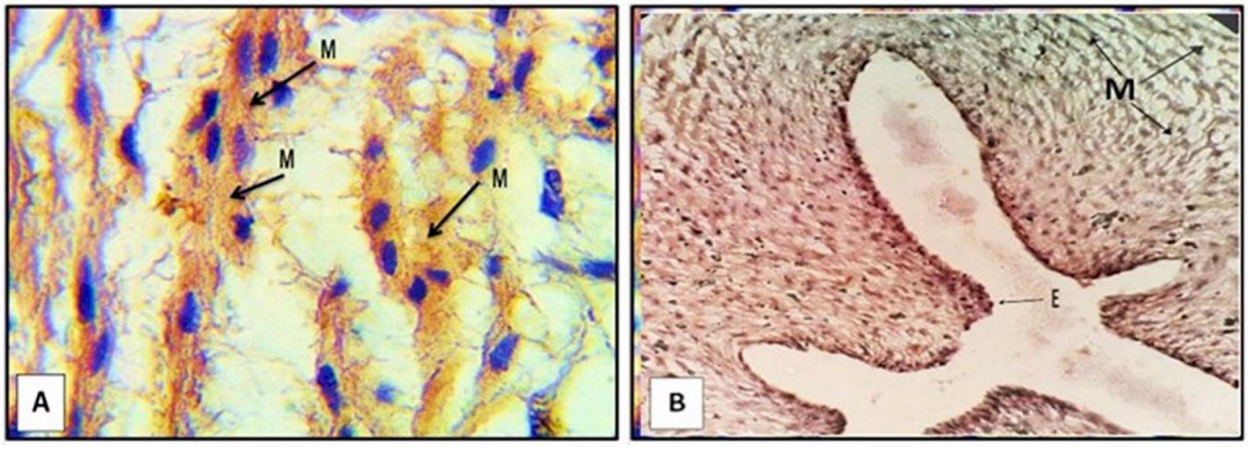

Fig 3. Cross section in umbilical artery with immunohistochemical staining with endothelin 1 antibody showing the positive expression of endothelin 1 in the cytoplasm of smooth muscle (M) and in endothelial cells (E). Endothelin1 Ab, PE group, magnification **(A)** x100, **(B)** x 40.

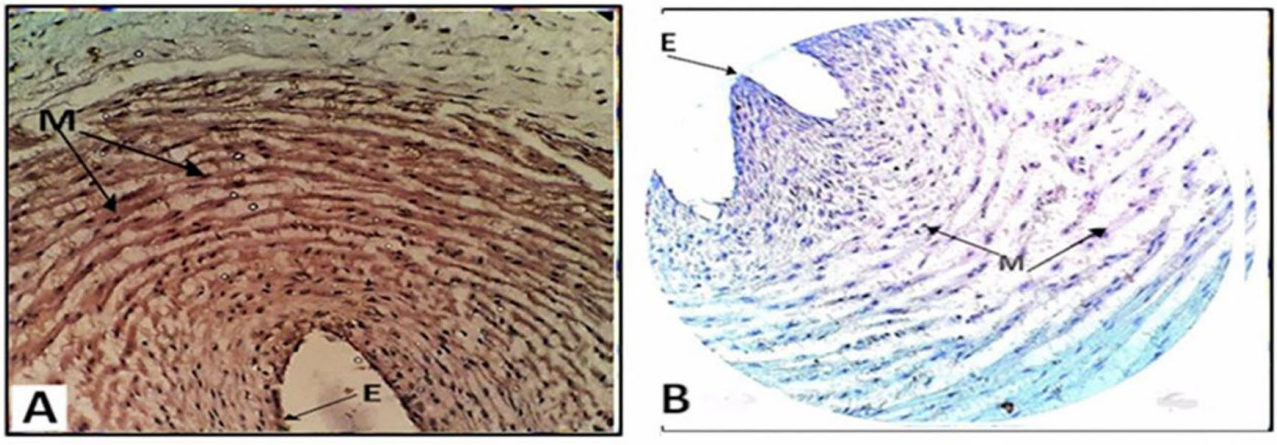

Fig 4. Cross section of umbilical artery showing intense brown pigmentation of ET1 immune-localization in the endothelial cells (E) and the smooth muscle (M) of the PE group **(A)** and the very weak reaction to the anti endothelin1 of the control group **(B)** endothelin1 Ab, magnification X400.

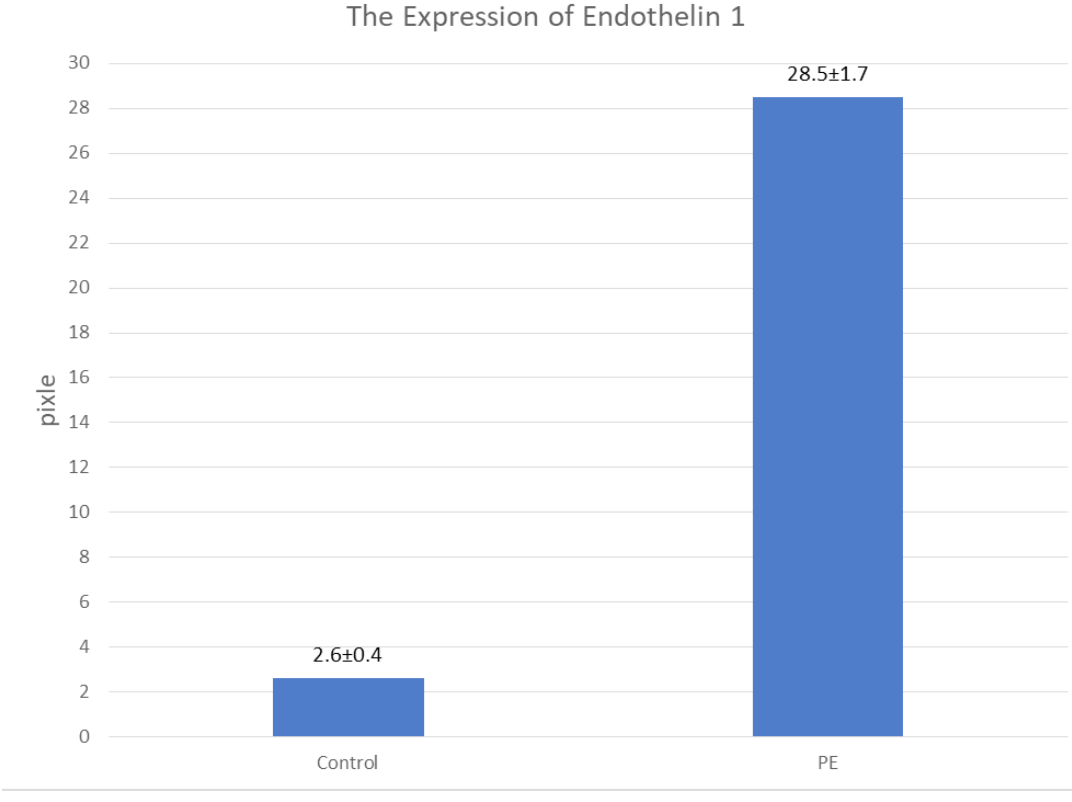

Fig 5. The expression of endothelin 1 in preeclampsia group with respect to control group presented as mean±SEM, p-value <0.05.

the plasma of maternal side, and was related to the influence of low pO2 in fetal blood.[24] In spontaneous labor, the concentration of ET1 in the umbilical cord and retroplacental blood plasma was ten times higher than those in the maternal peripheral blood suggesting that an elevation of the intrauterine secretion of endothelin-1 at delivery may stimulate the constriction of the blood vessels in the umbilical cord and placental bed.[25]

Endothelin 1 can also have a prolonged effect on blood pressure regulation The plasma level of ET1 can have substantial long-term effects on circulation and arterial pressure regulation. Thus, oversecretion of ET1 might have a significant role in mediating renal failure and hypertension observed in women with PE.[26] The present investigation might be the first study that demonstrated ET1 in umbilical vessels revealing that the strongest

staining pattern was detected in muscle & endothelial cells particularly in the arteries of PE samples. In PE the dysfunction of endothelial cells is responsible for the different presentations of PE like hypertension and proteinuria which results in a disturbance in the balance between substances that cause vascular dilatation and constriction.[27] Locally, ET1 a potent vasoconstrictor is produced by endothelial cells, increases smooth muscle contractility.[28] It is known that endothelin plays a significant role in the development of PE during pregnancy.[29] therefor, ET1 may stimulated a contractile response in arteries with damaged endothelium, and the severity of the damage in PE might potentiate the effect of ET1.[30] A previous study on pregnancies with intra uterine growth retardation revealed that ET-1 was localized diffusely in placental specimens from normal and IUGR pregnancies. The localization of ET-1 immunoreactivity was much higher in the endothelium of capillaries of villi as well as in the cells of the basal plate in the placenta of normal pregnancy than pregnancies with IUGR.[31]

ET-1 plays a significant role in regulating blood vessel function in all organ systems, ET1 elicited a presser response in vascular smooth muscle cells chiefly mediated by ETA receptors, and a depressor response chiefly mediated by nitric oxide released from endothelial cells through ETB receptors.[32] The present study has demonstrated a strong positivity of the vascular smooth muscle cells in the arterial wall which can lead to the dysregulation of vascular function leading to vascular constriction. Clinically, ET-1 has been implicated for the deterioration of renal function through loss of nephrin as Studies with an endothelin-1 (ET-1) receptor antagonist indicated that ET-1 was the main factor affecting loss of nephrin.glomerular endothelium was found to produce ET-1 when incubated with serum from PE patient, and recombinant ET-1 triggered nephrin shedding from podocytes.[33] which lead to the renal manifestation of preeclampsia which are characterized by proteinurea and hypertension.

ET-1 inhibits cell proliferation and vitality and triggers oxidative stress in the human placenta by altering the balance between oxidants and antioxidants forces in favor of oxidation[34] that's why we can clearly see changes in histological appearance of the umbilical cord of PE patients where the smooth muscle layer looses its uniform shape and shows cellular swelling which is a sign of cell injury. Therefore, according to this study, further research can be conducted on the benefit of blocking the ET-1 receptor in preventing the progression of preeclampsia to eclampsiawhich can save many mothers at risk from developing this disorder that carries high mortality rate.

The main limitation of this study is to get standardized immunohistochemical staining of the samples obtained so we need to observe the correct staining site in the tissue and ignore false positive random staining.and also to be able to preserve the tissue well to allow good preservation of the antigens as it is well known that a good immunohistochemical stain requires fresh tissue samples and the older the tissue the more loss of antigens.

CONCLUSION

It is concluded that ET1 is markedly increase in PE and may be the cause behind promoted vascular smooth muscle cell contraction and blood pressure elevation in PE.

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Conflict of interest statement

All the authors have contributed in this research, we have no conflict of interest to declare.

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Association of Oxcarbazepine-induced Cutaneous Adverse Drug Reactions with *HLA-B*15:02* Allele

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ABSTRACT

Objective: Oxcarbazepine (OXC) has similar structure and efficacy to carbamazepine (CBZ), but with fewer side effects. However, there have been only a few reports of serious cutaneous adverse reactions to OXC. *HLA-B*15:02*'s association with cutaneous adverse drug reactions (cADRs) induced by OXC is still inconsistent. This study investigated the incidence of cADRs that were induced by OXC and their association with the *HLA-B*15:02 allele* in Thais.

Methods: A retrospective cohort study of 494 patients receiving oxcarbazepine between January 2012 and January 2018 was undertaken. *HLA-B*15:02* testing had been carried out on 79 of the 494 patients.

Results: No incidents of serious cutaneous adverse reactions, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) were found. A 2.4% (12/494) of OXC-related cADRs was determined. Four out of six patients with maculopapular eruptions (MPE) were *HLA-B*15:02* positive. Patients who had the allele potentially developed OXC-induced MPE, with an odds ratio of 6.58 (95% CI 1.11-39.15, p=0.040). Only a history of other antiepileptic drug (AED) allergies demonstrated a significant risk factor of OXC-induced MPE.

Conclusion: Our research demonstrated that the association between the *HLA-B*15:02 allele* and MPE induced by OXC was significant. Patients with a history of other AED allergies were also at risk of developing OXC-induced MPE.

Keywords: Antiepileptics; association; *HLA-B*15:02*; cutaneous adverse drug reactions; human leukocyte antigen; incidence; maculopapular eruption; oxcarbazepine; Stevens-Johnson syndrome (Siriraj Med J 2020; 72: 174-180)

INTRODUCTION

Carbamazepine (CBZ) and oxcarbazepine (OXC) are both aromatic antiepileptic drugs (AEDs). They are utilized extensively as treatments for epilepsy, bipolar disorder, some neuropathic pain conditions, particularly trigeminal neuralgia.[1] However, severe cutaneous adverse drug reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) occasionally occur with these AEDs. The reactions may lead to long-term sequelae and fatal outcomes. According to the US Food and Drug Administration (FDA), adverse events declared to the World Health Organization and CBZ producers reveal that the rate of SJS and TEN induced by CBZ can be ten-fold higher in some Asian countries (4.1-5.9 per 10,000 patient-years of exposure) than in Europe and the USA (0.2-0.9).[2]

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Although many studies have since identified a similar relationship between *HLA-B*15:02* and SJS/TEN induced by CBZ, the allele does not appear to be a universal marker for CBZ-induced SJS/TEN, but it seems to be ethnically specific, for example, Japanese and Caucasian populations did not have this relationship.[3,4] Also, an association between the allele and CBZ-induced maculopapular eruptions (MPE) has been inconclusive. To illustrate, Sukasem et al. calculated an Odds ratio of 7.27 (95% CI 2.04-25.97) in Thais[5] while Locharernkul et al. reported an Odds ratio of 1.21 (95% CI 0.21-6.99) in Thais[6] and Man et al. demonstrated an Odds ratio of 0.84 (95% CI 0.15-4.51) in Han Chinese.[7]

The strong correlation between the *HLA-B*15:02* allele in Han Chinese patients and SJS induced by CBZ was first reported by Chung et al. in 2004.[8] Subsequently, several case-control studies have since confirmed the finding in Han Chinese, Malaysians and Thais[5,6,9,10] and suggested that screening of patients for the allele should be conducted prior to prescribing CBZ.[4,11] If a positive result was obtained, they should not be treated with CBZ.[12]

Oxcarbazepine (OXC), a member of the aromatic AEDs, has a similar structure and efficacy to carbamazepine (CBZ) but fewer side effects. OXC is considered as an alternative AED, but allergic cross-reactions between CBZ and OXC occur in approximately 1 in 4 patients.[13] The incidence of OXC-induced cutaneous adverse drug reactions (cADRs) was 2.0-2.7%.[14,15] However, there have been only a few reports of serious adverse reactions to OXC, and the inter-relationship between the allele and cADRs induced by OXC in Thais is still controversial. Although a recent case-control study reported a significant association between the *HLA-B*15:02 allele* and OXC-induced SJS, the positive predictive value was only 0.73%.[16] In current practice, however, doctors usually avoid OXC in *HLA-B*15:02* positive patients who may benefit from the AED.

Our study aims were to ascertain the incidence of cADRs caused by OXC and their association with the *HLA-B*15:02 allele* in the Thai population.

MATERIALS AND METHODS

After protocol approval was obtained from the Institutional Review Board of Siriraj Hospital (Si 400/2017), a retrospective cohort study was conducted. We included 494 patients who had received OXC at Siriraj Hospital between January 2012 and January 2018. The research team reviewed the patients' demographic data and the histories of drug and substance allergies documented in their electronic medical records.

Diagnosis of oxcarbazepine-induced cutaneous adverse drug reactions

The diagnoses of OXC-induced cADRs were obtained from the Adverse Drug Reaction and Counselling Unit at the hospital and a manual search of the medical records. This was based on the patients' histories and the clinical morphology of their skin reported by the attending physicians and dermatologists. Diagnoses of SCARs were reached by consensus by the physicians and dermatologists; they were based on the presence of life-threatening skin reactions, as evidenced by full-thickness epidermal necrosis, extensive erythema, and bullous epidermal detachment accompanied by mucosal involvement. SJS was defined as involving a body surface area detachment of ≤ 10%, while SJS/TEN overlap involved 10-30% of body surface area and TEN involved ≥ 30%.[17] Diagnoses of a drug reaction with eosinophilia and systemic symptoms (DRESS) were established using the criteria and scoring system of the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group; the reactions included acute rash, fever, enlarged lymph nodes, systemic involvement of at least 1 internal organ, blood count abnormalities, eosinophilia, and lymphadenopathy.[18] MPE were defined as self-limited, diffuse, erythematous macules and papules without blistering or pustulation.[14] As the cADRs usually develop within 3 months after exposure to OXC, the OXC-induced cADRs were diagnosed when skin lesions were identified within 3 months after the first prescription of OXC.

HLA-B genotyping

With the cooperation of the Division of Medical Genetics, Siriraj Hospital, 79 patients who had had a genomic test for *HLA-B*15:02* and received OXC were identified. Genomic DNA was extracted by QIAGEN quick DNA prep according to the manufacturer's protocol. DNA quality was measured by spectrophotometry. A modified PCR-SSCP was performed using sequence specific primers to amplify *HLA-B*15:02* locus using Real-time PCR (PCRmax Eco48, UK) followed by melting curve analysis.[19] Both negative and positive controls were run in parallel. A positive melting curve peak at 91.4 degree Celsius was interpreted as the presence of *HLA-B*15:02*. A positive melting curve peak at 77 degree Celsius is used as an internal control of PCR reaction. This PCR-SSCP cannot distinguish *HLA-B*15:02* from *HLA-B*15:13* and *HLA-B*15:25*, both of which are rarely present in Thai population.

Statistical analysis

Based on a prescription-event monitoring study,

the sample size of at least 252 patients used in this study was calculated from a 95% confidence interval (CI) of the OXC-induced cADRs incidence of 2.7% with an allowable error of 2%.[15] Statistical analyses were conducted on SPSS for Windows, version 18 (SPSS Inc., Chicago, IL, USA). Patients' clinical and demographic data were presented as number (%) or mean ± SD. The *HLA-B*15:02 allele* test results were reported as positive or negative. The risk factors related to cADRs induced by OXC were analyzed with Fisher's exact test of independence and the unpaired t-test. The association strength was determined by employing the odds ratio and its 95% confidence intervals (95% CI). A two-sided *p*-value of < 0.05 was defined as being statistically significant.

RESULTS

A total of 494 patients (194 males; 300 females; mean age = 59.0 ± 18.7 years) who received OXC between January 2012 and January 2018 were reviewed. Only 79 had a genomic DNA test for *HLA-B*15:02*.

Table 1 summarizes the 494 patients' demographic data (age and gender) and clinical characteristics (body mass index, indication for OXC usage). Only a history of other AED allergies (including gabapentin, pregabalin, carbamazepine, phenytoin and sodium valproate) demonstrated a significant association with OXC-induced MPE (Table 2). One out of nine patients with CBZ allergy also developed OXC-induced cADRs.

We found that 12 out of the 494 patients had had OXC-induced cADRs; six patients had had a genomic test for *HLA-B*15:02*, while the other 6 had not. There were no reports of SCARs. As a result, the incidence of OXC-induced cADRs in this study was 2.4% (12/494).

Of the 79 patients who underwent genomic testing, 21 (26.6%) were positive for *HLA-B*15:02*. Four out of the six patients with OXC-induced cADRs were *HLA-B*15:02* positive, with a positive predictive value of 19% and a negative predictive value of 96.6%. Patients who had the allele potentially developed OXC-induced cADRs, having an odds ratio of 6.58 (95% CI 1.11-39.15, p = 0.040; Table 3). The sensitivity and specificity of the allele predicting OXC-induced cADRs were 66.6% and 76.7%, respectively.

The clinical characteristics of the 12 individuals with OXC-induced MPE are presented at Table 4. The OXC-induced cADRs patients aged from 21 to 84 years and maximal tolerable dose of OXC ranged from 150-1200 mg/day. The cADRs could occur as early as 2 days or up to 34 days after the first dose.

TABLE 1. Demographic and clinical characteristics of patients receiving oxcarbazepine (OXC).

Characteristics	N = 494
Gender	
Male	194 (39.3)
Female	300 (60.7)
Age (yr)	59.0 ± 18.7
Body mass index (kg/m^2)	25.1 ± 5.7
OXC indication	
Neuropathic pain	407 (82.4)
Epilepsy	30 (6.1)
Mood disorder	57 (11.5)
History of drug allergy	
Other drugs	123 (24.9)
Other AEDs	20 (4.0)

The data are presented as mean ± standard deviation or n (%).
Abbreviations: AEDs = antiepileptic drugs; OXC = oxcarbazepine

TABLE 2. Potential risk factors associated with OXC-induced cADRs.

Risk factors	Number of patients		Odds ratio	95% CI	*p*-value
	OXC-induced cADRs (N = 12)	OXC-tolerant (N = 482)			
Male	4 (33.3)	190 (39.4)	1.30	0.39-4.38	0.772
BMI	23.2 ± 4.9	25.1 ± 5.7	-	-	0.255
History of other drug allergies	4 (33.3)	119 (24.7)	1.53	0.45-5.16	0.504
History of other AED allergies	2 (16.7)	18 (3.73)	5.16	1.05-25.27	0.043*

The data are presented as mean ± standard deviation or n (%). *$p < 0.05$ was statistically significant

Abbreviations: AED = antiepileptic drug; BMI = body mass index; cADRs = cutaneous adverse drug reactions; CI = confidence interval; OXC = oxcarbazepine

TABLE 3. Association of the *HLA-B*15:02 allele* with OXC-induced cADRs.

HLA-B 15:02 allele*	Number of patients		Odds ratio	95% CI	Positive likelihood ratio	Negative likelihood ratio	*p*-value
	OXC-induced cADRs (N = 6)	OXC-tolerant (N = 73)					
Positive	4	17	6.58	1.11-39.15	2.86	0.43	0.040*
Negative	2	56					

The data are presented as n (%). *$p < 0.05$ was statistically significant

Sensitivity 66.6%; Specificity 76.7%; Positive predictive value 19%; Negative predictive value 96.6%

Abbreviations: cADRs = cutaneous adverse drug reactions; CI = confidence interval; OXC = oxcarbazepine

TABLE 4. Clinical characteristics of patients with OXC-induced MPE.

No.	Sex	Age	Indication	Maximum dose (mg)	*HLA-B*15:02*	Latency (days)	History of other drug allergies
1	F	84	Pain	900	Negative	30	No
2	F	54	Pain	1,200	Positive	28	No
3	M	44	Pain	300	Positive	4	No
4	M	32	Pain	450	Positive	14	No
5	F	52	Pain	900	Positive	14	Carbamazepine
6	M	21	Pain	150	Negative	3	No
7	F	35	Pain	1,200	NA	2	No
8	F	74	Pain	600	NA	NA	Actifed®
9	F	35	Pain	600	NA	9	No
10	F	39	Pain	300	NA	10	Phenytoin
11	F	43	Pain	600	NA	NA	No
12	M	64	Pain	900	NA	34	Ceftriaxone

Abbreviations: F = Female; M = Male; NA = not available

DISCUSSION

Oxcarbazepine is considered as an alternative AED, and there is evidence to suggest that it has a safer profile, and a better tolerance than CBZ. On the other hand, OXC and CBZ have an allergic cross-reaction of about 25%-30%.[13,20]

Incidence of OXC-induced cADRs in Thais

The present study found the overall incidence of OXC-induced cADRs was 2.4% (12/494), while that of SJS/TEN induced by OXC was 0% (0/494). The latter figure was comparable to that published in the 2016-version of the Thai-FDA's annual report on ADRs (the incidence of OXC-induced SJS/TEN was 0.02%). Moreover, this study's overall figure of 2.4% for OXC-induced cADRs was similar to the 2% incidence found in Han Chinese;[14] and the present study's figure of 0% for OXC-induced SJS/TEN was lower than corresponding figure reported in Taiwanese, which was 0.08% (8.26/10,000 new users).[16] The findings of the current study therefore confirm previous reports that the incidence of SCARs is lower with OXC than CBZ.

*Association between HLA-B*15:02 and OXC-induced cADRs*

The present research determined that there is a correlation between the *HLA-B*15:02 allele* in the Thai population and MPE induced by OXC, the odds ratio being 6.58 (95% CI 1.11-39.15; p = 0.040). A similar result, but not statistically significant, was found in a case-control association study by Hu et al.[21] (odds ratio 6.4; 95% CI 0.55-74.89; p = 0.294). We therefore suggest that if a Thai patient carries the allele, the attending physician should take the risk of OXC-induced MPE into consideration. The prescribing of alternative non-aromatic AEDs would be prudent; however, if OXC is prescribed, it should be done with caution, with the patient being informed about the risk of drug allergies and requested to closely observe for any symptoms to ensure the earliest detection of potential problems.

Nevertheless, two studies in Han Chinese population determined that the inter-relationship between the *HLA-B*15:02* allele and OXC-induced cADRs is not significant; rather, they identified two other genotypes (*HLA-B*1302*[14] and H*LA-B*3802*[22]) as risk factors. Similarly, a study by Moon et al.[23] demonstrated that two different genotypes, *HLA-B*40:02* and *HLA-DRBI*04:03*, are risk factors among Koreans. The results of those three studies show that different genomic types might be specifically associated with particular ethnic populations.

*Recommendation of HLA-B*15:02 testing prior to OXC prescription*

Many studies have found no correlation between *HLA-B*15:02* and SJS/TEN induced by OXC.[14,22,23] However, a recent prospective study reported that, in Han Chinese and Thais, the allele is significantly related to OXC-induced SJS/TEN (odds ratio 27.90; 95% CI 7.84-99.23, positive predictive value 0.73%).[16] This supports a concern of avoiding OXC for patients with *HLA-B*15:02* allele, although OXC-induced SJS/TEN is less severe and has a lower incidence than CBZ-induced SJS/TEN.[16] This advice may not be applicable for some populations as *HLA-B*15:02* is very commonly found in certain populations in Asia[3] (5.7%-14.5% in Han Chinese, 12%-15.7% in Malays and 15.9% in Thais[24]).

In addition, there have also been reports of an allergic cross-reaction between CBZ and OXC. In the present study, we found 1/9 case who had an allergy to CBZ and OXC, and who was *HLA-B*15:02* positive.

Regarding other predicting factors, a study by He et al.[14] found that a history of AED or non-AED allergies were strong predicting factors for OXC-induced cADRs, but especially an allergy to other AEDs (OR 121.23, 95% CI 3.99-3686.59, p = 0.005). However, our study found a significant association with only a history of other AED allergies (OR 5.16, 95% CI 1.05-25.27, p = 0.043), but not with a history of non-AED allergies (OR 1.53, 95% CI 0.45-5.16, p = 0.504).

Taking all this into consideration, OXC-induced cADRs have a minor impact on allergic patients, who can simply discontinue use of the drug. Given that the positive predictive value of the allele is only 19% for MPE and 0.73% for SJS/TEN[16], *HLA-B*15:02* test before prescribing OXC is still recommended in order to surveil SCARs. There may be patients who test positive to genomic testing but may still benefit from sodium channel blocking antiepileptics to treat their pain, such as those with trigeminal neuralgia and painful tonic spasm.[25] *HLA-B*15:02* has a high prevalence in Thai populations, so it is reasonable to prescribe OXC rather than CBZ with good patient-education, close monitoring of MPE and discontinue the drug immediately if a rash occurs.

Limitations

The incidence of OXC-induced cADRs may be higher than reported due to undocumented histories of rash or unclear medical records (which were excluded). Moreover, some individuals were lost to follow-up after receiving the drug, while others did not register at the

ADR center, resulting in their cases not being recorded in the hospital's electronic record system.

In addition, there has been no standard recommendation to test for *HLA-B*15:02* prior to prescribe OXC. The genomic testing is also costly and time-consuming, with the results taking 1-2 weeks to be reported. Therefore, only 79/494 patients had been tested for *HLA-B*15:02*.

This study also had too small a sample size to detect the incidence of SCARs induced by OXC. Thus, we support the conduct of a further study to establish the inter-relationship between the allele and OXC-induced cADRs/SJS/TEN/DRESS by using a larger sample size and a multicenter design in Thailand.

Our study demonstrated that the association between the *HLA-B*15:02 allele* and MPE induced by OXC is significant. Patients with a history of other AED allergies also had an increased risk of developing OXC-induced MPE. However, a larger sample size and multicenter study should be conducted.

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The First Robotic Bariatric Surgery Performed in Thailand – Surgical Techniques and Review of the Literature

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ABSTRACT

Morbid obesity is associated with multiple life-threatening comorbidities. Bariatric surgery is the most effective intervention to achieve the long-term weight loss required to reverse many of these comorbid conditions. Laparoscopic bariatric surgery is the current gold standard approach; however the robotic approach has potential intraoperative and postoperative advantages that may be realized if limitations to instrument torque effect are overcome. We review the literature about the robotic bariatric surgery and describe our first robotic sleeve gastrectomy (RSG) and a single docking operative approach to robotic Roux-en-Y gastric bypass (RRYGB) in Siriraj Hospital, and also the first in Thailand. We demonstrate the operative room setup, the port sites, the technical details, and the key step illustrations, that both operative procedures were performed using the da Vinci® Si platform. According to the literature review, a robotic approach to bariatric surgery is an alternative option with comparable outcomes to laparoscopic approach and the potential for intraoperative and postoperative advantages. It is safe, feasible, and provides good clinical outcomes that are comparable to a conventional laparoscopic method.

Keywords: Bariatric surgery; robotic bariatric surgery; robotic Roux-en-Y gastric bypass; robotic sleeve gastrectomy; robotic surgery (Siriraj Med J 2020; 72: 181-187)

INTRODUCTION

Morbid obesity has become a serious worldwide health issue because it is associated with multiple life-threatening comorbidities. Bariatric surgery is considered to be the most effective strategy to achieve long-term and sustained meaningful weight loss for obese patients with very low postoperative morbidity and mortality. Although conventional laparoscopy is the current gold standard for almost all bariatric procedures, there are some limitations of the laparoscopic approach, especially in super morbidly obese patients. Laparoscopic procedures in the super morbidly obese can be physically challenging for the surgeon and for the equipment due to limited torque effect of instruments in patients with hepatomegaly, increased intraabdominal fat, and extremely thick abdominal walls.[1-3]

Robotic surgical systems were introduced in 1997 to overcome the disadvantages of a traditional laparoscopic approach. The application of robotic surgery has increased significantly in the field of general surgery and has become

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more popular in bariatric procedures. The advantages of using robotic systems include better surgeon's ergonomics, a magnified 3D imaging system from the very stable camera controlled by surgeon, the articulated robotic wrists that increase degrees of movement degree in enclosed spaces, and precision in tissue manipulation with tremor filtration for the surgeon. Potential benefits to our patients include safer procedures, less complications, less pain, and faster recovery, while the other benefits of minimally-invasive surgery are preserved. Horgan and Vanuno described the first Roux-en-Y gastric bypass (RYGB) performing by the robotic system in 2001, and Mohr and team reported the technique of a totally robotic RYGB with a single docking position in 2005.[1,3-7]

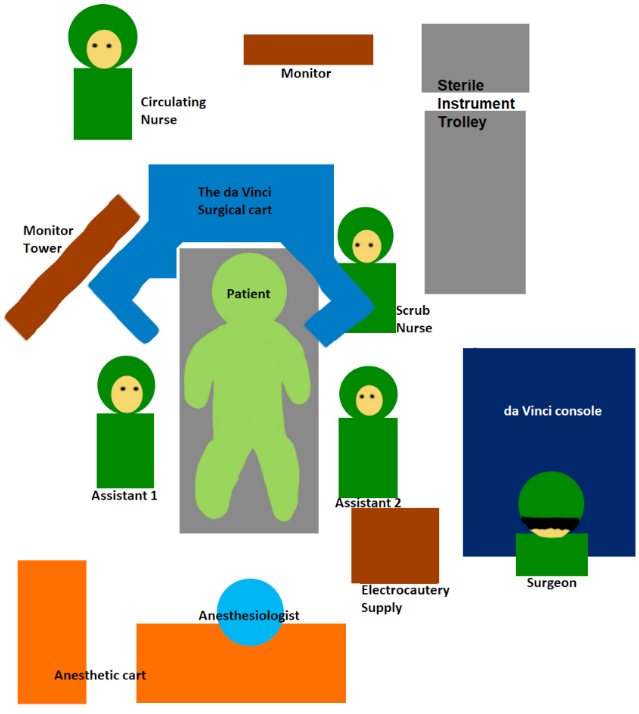

Fig 1. Operating room set up for robotic bariatric procedures.

In this manuscript, we describe our initial experiences with a robotic approach to bariatric surgery at Siriraj Hospital, Bangkok, Thailand. We present our step-by-step single docking robotic approach to operate sleeve gastrectomy and Roux-en-Y gastric bypass by the da Vinci® Si robotic system (Intuitive Surgical, Sunnyvale, CA, USA).

The Surgical Techniques of Robotic Sleeve Gastrectomy (RSG):

The patient was positioned supine with both arms adduction. A 36-French orogastric tube was placed. A Veress needle was used to enter the abdomen at Palmer's point and the abdomen was insufflated with carbon dioxide gas to 15-18 mmHg. A 12-mm camera port was placed 18 cm inferior to the xiphoid and 4 cm to the left of midline using an Optiview trocar and a 10-mm zero-degree laparoscope in visual entry fashion. After entry, this was exchanged for a 30-degree laparoscope. Under direct visualization, the Veress needle was removed after confirming no injury was sustained upon insufflation. Additional 8-mm ports were placed 2 cm below the right costal margin in the midclavicular line, and 2 cm below the left costal margin in the anterior axillary line. Finally, a 15-mm laparoscopic assistant's port was placed 18 cm inferior to the xiphoid and 2 cm to the right of midline. Another small stab incision was made in the epigastric area, 1 cm right of midline, then the strong arm Nathanson liver retractor was advanced through this incision to elevate the left hepatic lobe so that the inferior phrenic vein was clearly identified. The patient was set in reverse Trendelenburg position. Two working arms of the da Vinci® Si system were docked to the 8-mm port sites, and an additional arm was docked to the 12-mm camera port. The robotic Harmonic shears were used to divide

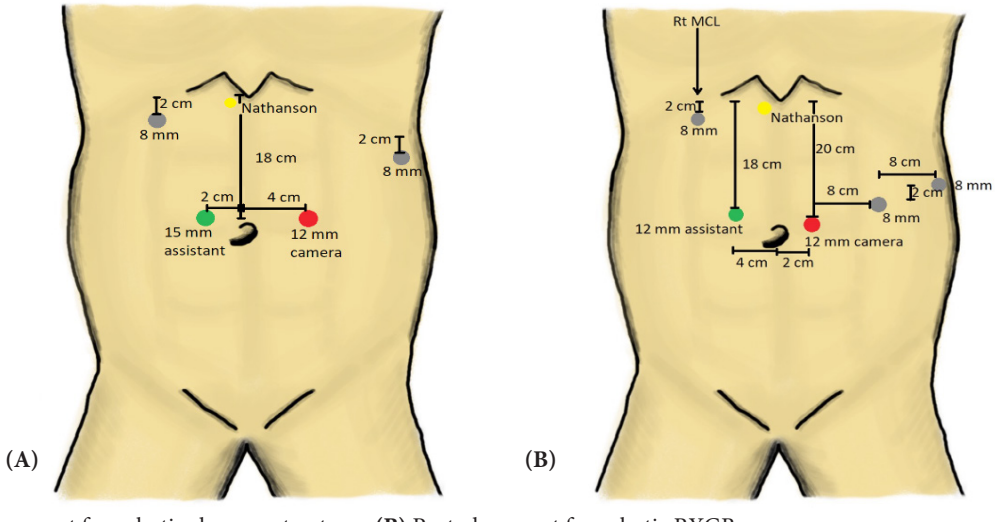

Fig 2. **(A)** Port placement for robotic sleeve gastrectomy **(B)** Port placement for robotic RYGB

the greater omentum from the gastric greater curvature, from 6 cm proximal to the pyloric ring to the angle of His. The short gastric arteries were also ligated with Harmonic shears, double-shot technique, during dissection.

Using the OG tube as a guide, the robotic hook cautery was used to mark the planned line of resection. The iDrive™ Stapling System (Medtronic, Dublin, Ireland) was then introduced via the laparoscopic assistant's port, and using multiple fires of 60-mm iDrive™ black and purple cartridges, the gastric greater curvature was stapled off. The posterior wall of the gastric tube was secured to the posterior fat pad with interrupted 2-0 Ti-Cron stitches (Medtronic, Minneapolis, USA).

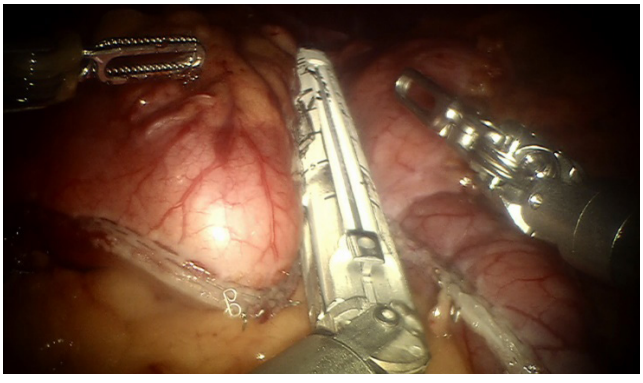

Fig 3. Gastric division by autostapler via assistant port.

Hemostasis was checked then the resected stomach was removed using an EndoBag (Medtronic, Dublin, Ireland) via the 15-mm port incision. The 12 and 15-mm port sites were closed using 1-0 Vicryl suture on a suture passer. All ports were removed, the robotic system was undocked, and the skin was closed in standard fashion.

The Surgical Techniques of Robotic Roux-En-Y Gastric Bypass (RRYGB):

The patient was positioned supine with both arms tucked. A 36-French orogastric tube was placed. A Veress needle was used to enter the abdomen at Palmer's point and the abdomen was insufflated with carbon dioxide gas to 15-18 mmHg. A 12-mm camera port was placed 20 cm inferior to the xiphoid and 2 cm to the left of midline using an Optiview trocar and a 10-mm zero-degree laparoscope in visual entry fashion. The camera was exchanged for a 30-degree laparoscope, the Veress needle was removed, then two additional 8-mm working ports were placed to the left of the camera port; the first with 8 cm of lateral clearance and approximately 2 cm superior to the camera port, the second at 8 cm lateral to and 2 cm superior to the former 8-mm port. An additional 8-mm working port was placed in the right upper quadrant, 2 cm below right costal margin in midclavicular line, and then a 12-mm laparoscopic assistant's port was placed 18 cm inferior to the xiphoid and 4 cm to the right of midline.

Another small stab incision was made in the epigastric area, 1 cm right of midline, and the strong arm Nathanson liver retractor was advanced through this incision to elevate the left hepatic lobe so that the inferior phrenic vein was clearly identified. Using a laparoscopic Harmonic scalpel, the greater omentum was split in a left paramedian plane to 1 cm away from the transverse colon. While the assistant retracted the mesocolon caudally, the Ligament of Treitz was identified. Two interrupted 3-0 Vicryl stitches were placed to mark the jejunum at 100 cm and 200 cm. The loop of jejunum marked at 100 cm distal to the Treitz's ligament was then sutured to the anterior gastric antral wall using two interrupted 3-0 Vicryl stitches.

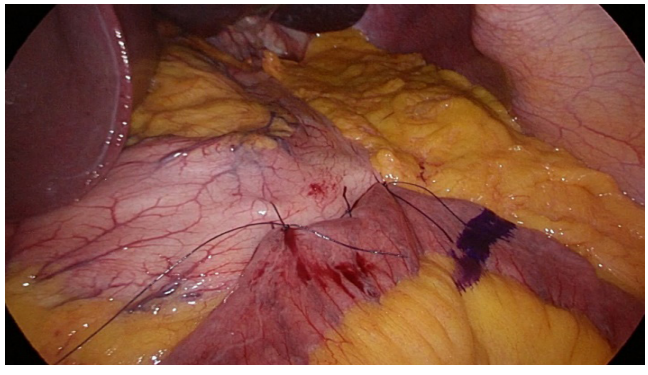

Fig 4. The marked jejunal loop was fixed to gastric antrum.

The patient was then placed in reverse Trendelenburg position and three working arms and a camera arm of the da Vinci Si® robotic system were docked to the 8-mm ports and the 12-mm camera port, respectively. Using the robotic hook cautery, the lesser omentum was entered at the level of the second vein (about 6 cm from the esophagogastric junction) to create the gastric pouch. Then the iDrive™ Stapling System with a 45-mm purple cartridge was introduced via the laparoscopic assistant's port and fired horizontally across the stomach from the defect in the lesser omentum. Sequential vertical fires of the iDriveTM Stapling System with 60-mm purple cartridges were used to carry the staple line upward to a point just lateral to the angle of His, ensuring complete gastrogastric division.

Using the hook electrocautery, enterotomies were made in the posterior wall of the gastric pouch and the jejunum that had been previously tacked to the greater curvature of stomach. The tacking stitches were removed and a 45-mm purple cartridge in the iDrive™ Stapling System was used to create a 2-cm linear gastrojejunostomy.

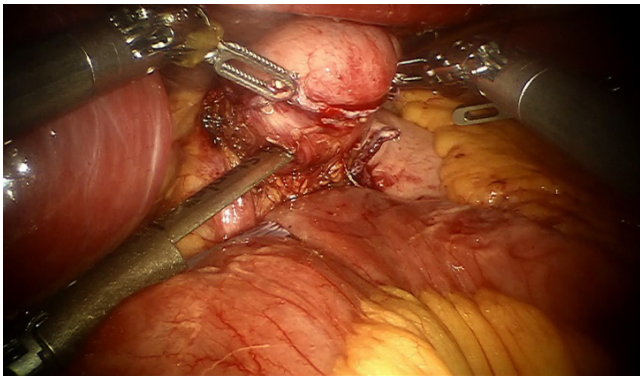

Fig 5. Gastrojejunostomy creation using the iDrive™ Stapling System with 45-mm purple cartridge.

A 60-mm tan cartridge was used to divide the biliopancreatic limb just proximal to the gastrojejunostomy. The hook cautery was used to create enterotomies in the distal biliopancreatic limb and at the site of the jejunal marking stitch that had been previously placed at 200 cm beyond the Ligament of Treitz. Using a 45-mm tan cartridge, a 45-mm stapled jejunojejunostomy was made between the biliopancreatic limb and jejunum to create a 100-cm Roux limb. The enterotomy site was closed using continuous 3-0 Vicryl suture and the mesenteric defect was closed to its base with continuous 2-0 Ti-Cron suture. Reinforcing and anti-kink stitches were placed between the biliopancreatic and Roux limbs using 3-0 Vicryl suture.

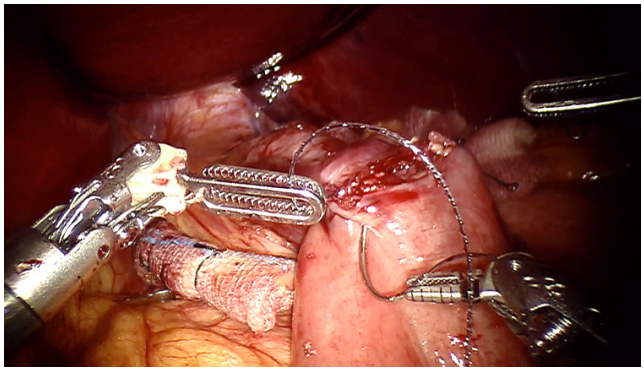

Fig 6. Gastrojejunostomy defect closure by intracorporeal robotic suturing.

The gastrojejunal enterotomy site was closed using running 3-0 absorbable V-loc suture (Medtronic, Dublin, Ireland) and the corners were reinforced with interrupted 2-0 Ti-Cron stitches. A leak test was then performed by instilling 50 mL of dilute methylene blue solution (2 mL per 100 mL of normal saline solution) into the orogastric tube. The Petersen's defect was closed by suturing the mesentery of the Roux limb to the transverse mesocolon using running 2-0 Ti-Cron suture. The liver retractor was removed and a 10-French JP drain was placed near the gastrojejunostomy through the left upper quadrant port site. The 12 and 15-mm port sites were closed using 1-0 Vicryl on a suture passer. All ports were removed, the robotic system was undocked, and the skin was closed in standard fashion.

The Siriraj's Experience in Robotic Surgery and Robotic Bariatric Surgery

About the first robotic platform in Siriraj Hospital, the da Vinci® S robot was purchased in 2007 which the main users were the urological surgeons. The robotic operation for general surgery field in Siriraj Hospital was started in 2008 then the robotic approach in general surgery were developed consistently. Robotic-assisted complete excision of choledochal cyst type I with hepaticojejunostomy was the first international report of our institute by Minimally Invasive Surgery team in 2010. The da Vinci® Si Surgical System was our second model that introduced to Siriraj Hospital since 2012, and the latest one, da Vinci® Xi robotic platform, was imported to our center in August 2019. Most of the general surgery cases operated by robotic approach were funded by Siriraj Foundation for educational purpose in general surgery training program.[8]

Our first robotic operations for bariatric surgery in Siriraj Hospital, and also first in Thailand, were performed on March 6th, 2017 by Dr. Voraboot Taweerutchana and team. Our first patient for robotic sleeve gastrectomy is a 26-year-old female with body weight 93 kg (BMI 40.79 kg/m^2) and no comorbid disease. And our first patient for robotic Roux-en-Y gastric bypass is a 38-year-old woman who weighed 110 kg (BMI 40.40 kg/m^2) and comorbidity of dyslipidemia. In our first two patients undergoing robotic bariatric surgery, total operative time for robotic SG and robotic RYGB was 160 and 285 minutes, respectively. The estimated blood loss was 20 mL in both cases. Their postoperative pain was managed by intravenous PCA routinely by the acute pain service team. The postoperative average pain scores, visual analog scale, at 2 hours, 12 hours, and 24 hours were 10, 5.5, and 4.58 in the patient who underwent RSG, and the scores were 9, 5.4, and 4.2 in the patient who underwent RRYGB. Intravenous PCA can be discontinued on postoperative day 2 in RSG and day 3 in RRYGB patients. No further requirement of oral paracetamol after 2-day around-the-clock prescription in both patients. The patients were both discharged from the hospital on postoperative day 4. No open conversion, immediate complication, or 30-day mortality was observed. The total hospital costs were 336,629 THB (Thai baht) and 402,333 THB for robotic

SG and robotic RYGB, respectively. Excess weight loss (EWL) at 6 months post robotic SG and robotic RYGB were 60% and 52%, and at 12 months were 60% and 65%, respectively. The comorbidity of dyslipidemia in the patient who underwent RRYGB has significantly improved and oral medication has been discontinued.

One of the challenges of the da Vinci® Si platform is the inability to adjust the craniocaudal tilt of the operative table once the robot has been docked to the port sites, which makes it difficult to perform multi-quadrant procedures, like Roux-en-Y gastric bypass. Therefore, in our institute, we initiated the robotic RYGB with the single docking technique by performing the infracolic phase using a laparoscopic approach, followed by a robotic approach to the supracolic phase of the procedure, that considered as the hybrid robotic operation. In the infracolic phase, we placed marking stitches to the jejunum at 100 cm and 200 cm from Treitz's ligament to identify the site of the biliopancreatic limb and Roux limb to avoid the need for running the small bowel once the robotic system has been docked. Then we secured the jejunum to the greater curvature of stomach, making it easier to grasp the Roux limb while performing the gastrojejunostomy with robotic instruments in the supracolic phase. Nowadays, we perform the totally robotic RYGB that infra- and supracolic phases performed under the reverse Trendelenburg position with hand-sewn gastrojejunostomy anastomosis by that the report is now in process of the data collection and analysis.

Laparoscopic Versus Robotic Approach to Bariatric Surgery

The field of bariatric surgery has evolved worldwide in the recent decades due to its excellent results in treating morbid obesity and its related comorbidities. With the introduction of robotic surgery in recent years to the practice of minimally invasive general surgeons, efficient applications of robotic technology to bariatric surgery have been sought. The advanced technology of the robotic system enables the surgeon to operate the complex surgical tasks, e.g. the hand-sewn gastrojejunostomy in Roux-en-Y gastric bypass with more precision.[1,2,6,9]

Laparoscopic RYGB remains a complex bariatric procedure with a steep learning curve. It requires advanced laparoscopic skills, such as intracorporeal suturing, knot tying for the multiple anastomoses, fine manipulation in various abdominal compartments, and redoubled abdominal torque causing the operator's fatigue. In the former reports, the learning curve for robotic RYGB seems to be shorter than that for laparoscopic RYGB, 10-20 cases versus ≥ 100 cases, respectively.[4,5,10,11]

The disadvantages of robotic surgery are the larger sized ports than used in traditional laparoscopic surgery (8-mm versus 5-mm) and loss of tactile sensation and force feedback, which may lead to bowel wall or visceral injury during manipulation. The benefits of the robotic approach over laparoscopic bariatric surgery are still debated and controversial. Multiple case series have shown the feasibility and clinical safety of robotic bariatric surgery, and also shown comparable results with laparoscopic bariatric procedures, but some authors believe that there is no advantage over standard laparoscopic techniques.[1,2,6,9,10]

In our initial experience at Siriraj Hospital, the results of robotic bariatric surgery demonstrated good clinical outcomes. No immediate complication, leakage, or mortality was detected in 30-day postoperative follow-up. Excess weight loss and resolution of comorbidity at 6- and 12-months were comparable to a conventional laparoscopic approach.

In terms of weight reduction, the robotic approach has comparable results to laparoscopic bariatric surgery in previously published reports. One meta-analysis showed EWL of 34-67% at 6 months and 48-67.3% at 12 months in the laparoscopic sleeve gastrectomy group, while EWL was comparable at 39-66% at 6 months and 48.89-65.5% at 12 months in the robotic approach for sleeve gastrectomy. Other reports described excess BMI loss after Roux-en-Y gastric bypass at 1 month of 26.2% in the robotic group and 26.3% in the laparoscopic group, and at 12 months, 79.7% in the robotic group and 83.9% in the laparoscopic group. In our cases, EWL at 12 months was 60% in our RSG patient and 65% in our RRYGB patient.[12,13]

Systematic reviews and meta-analysis have shown no significant differences between robotic and laparoscopic bariatric procedures with regards to reoperation, open conversion, the hospital stay interval, overall postoperative complications, major complications, and mortality, however there are some differences in outcomes as follows.[1,4,9,13] Anastomotic leakage were significantly decreased overall after robotic bariatric procedures compared with laparoscopic procedures (OR 0.5, $p = 0.005$) and totally-robotic RYGB compared with laparoscopic RYGB (OR 0.22, $p = 0.001$). The additive learning effect from laparoscopic cases performed prior to the introduction of robotics and more precision in anastomosis suturing by robotic systems may be the reasons for these results. Moreover, minor complication rates were significantly decreased after totally-robotic RYGB compared with laparoscopic RYGB (OR 0.68, $p = 0.04$). Robotic sleeve gastrectomy reduced the postoperative bleeding (0.16% vs. 0.43%; $p < 0.001$) and stricture (0.19% vs. 0.33%;

$p = 0.04$) significantly when compared with traditional laparoscopic sleeve gastrectomy.[1,2,14,15]

In review of the literature, no significant difference of the operative time was found between totally-robotic RYGB and laparoscopic RYGB ($p = 0.42$). On the other hand, there was increased operative time for robotic-assisted RYGB versus laparoscopic RYGB (158.29 ± 65 vs. 120.17 ± 56; $P < 0.001$), and for robotic sleeve gastrectomy compared with laparoscopic sleeve gastrectomy (102.58 ± 46 vs. 73.38 ± 36; $P < 0.001$). A robotic set up time did not vary significantly and remained at a mean of 13 ± 4 min in the previous report. Finally, we believe that the operative time in robotic approach can be reduced once the learning curve is overcome, just as with other robotic procedures.[1,13-15]

Although robotic procedures seem to be more expensive than laparoscopic surgery due to initial purchase costs of the robot and the robotic instruments and accessories, as well as yearly maintenance fees that are associated with significant costs. From the University Health System Consortium (UHC) Clinical Database, the mean cost of robotic gastric bypass was $12,670, versus $10,105 for laparoscopic RYGB ($p < 0.05$). Moreover, the mean costs of robotic and laparoscopic sleeve gastrectomy were $10,556 versus $8,795 ($p < 0.05$), respectively. Despite this, previous analyses have concluded that robotic RYGB can be cost effective as a result of a decrease of costly anastomotic complications and avoiding stapler use in the case of hand-sewn anastomoses. In the event of postoperative leak, readmission is costly, and these authors demonstrated higher leak rates in the laparoscopic group.[1,16,17]

The Future Trends in Robotic Bariatric Surgery

The new medical technologies, included the robotic surgery system, are always updated to provide the patients' benefit. Nevertheless, the overall costs of robotic approach for bariatric surgery seemed to be more expensive than the laparoscopic surgery, which is the standard treatment in this era, and there were a few evidences to support the clear benefit of robot over the laparoscopic one, the usages of robot in bariatric surgery remained controversial, especially in the expert bariatric surgeons who familiar with their laparoscopic skills.

As the oldest and largest hospital and medical school in Thailand, Siriraj Hospital cannot avert the robotic surgery due to academic purposes. To utilize the maximal technology abilities, to clearify the cost-effectiveness of the robotic approach by the data analyses and publications, and to manage the efficient usages of the robotic system are Siriraj's duties. The robotic bariatric surgery cases will be maintained for these objectives in Siriraj Hospital. Although Siriraj Foundation was the main supporter in funding of robotic approach in general surgery cases, the effective hospital resource management can also reduce the overall robotic surgery costs, for example, to increase the robotic case volume and the patient flow.[8]

Furthermore, revisional bariatric surgery may be a field that robotic bariatric surgery becomes a favored approach, because of its ability to provide fine movement and a high-degree of articulation in a challenging operative field. These special properties of the robotic system facilitate the surgeon's ability to perform a difficult operation more precisely and comfortably, despite intraabdominal adhesions and distorted anatomy.

Although there were some potential advantages of the robotic approach in bariatric surgery from the previous studies as mentioned above, there have been no well-designed randomized trials to compare the outcomes between conventional laparoscopic bariatric surgery with the robotic surgery. To improve the value of this research field, a large-scale comparative study using a randomized controlled trial technique should be considered. In the future, if the clear benefits of using robots in bariatric surgery are well-supported, the robotic system investors will be increased in the market and the overall robotic costs will be reduced. Moreover, the treatment costs by robotic system may be concerned and covered by the health insurance system.

CONCLUSION

Using robotic approach in bariatric surgery is still controversial due to its cost and availability. The operative room setup, the port sites, the instruments, the technical details, and the key step illustrations for robotic SG and robotic RYGB are described by Siriraj's experiences. From the current evidences, a robotic approach for bariatric surgery is demonstrated to be a feasible alternative to laparoscopic bariatric surgery. It is shown to be equally as effective and safe as a laparoscopic approach, and provides comparable clinical outcomes to the conventional laparoscopic method.

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Effectiveness of Herbal Medicine in Renal Lithiasis: A Review

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ABSTRACT

The renal lithiasis is a frequent disease that affect between 4-15% of worldwide population with a high percentage of recurrences. The composition of the stone is variated, but, more than 80% of uroliths are of calcium oxalate. The mechanisms involved in the formation of calcific stones are not fully understood and the available treatment not permit the prevention and destruction of the stones at same time. For these reasons, many studies have been focused to understand the mechanism involved in the renal lithiasis and in the development the new drugs for the treatment and prevention of this pathology and its recurrences. In this paper, it is shown a review about formation of calcific stones, their treatment and the effectiveness of the herbal medicine as alternative treatment. Also, a list of antilithiatic remedies of cuban herbal medicine is showed.

Keywords: Renal lithiasis; pharmacology; therapeutic; herbal medicine (Siriraj Med J 2020; 72: 188-194)

INTRODUCTION

Renal lithiasis can be defined as the deposition of stones in urinary tract due to an alteration of the normal crystallization conditions of urine.[1] It is explained through of the loss of the equilibrium between promoters and inhibitors of the crystallization,[2] urine composition and renal morphoanatomy.[3]

Currently, it is the third most frequent urological disease after urinary tract infections and prostate problems.[4] It has a prevalence that ranges between 4-15% of the world population[5] and a high recurrence rate, that is, the probability of repeating a renal lithiasis episode is 40% after 5 years of the first calculi and 60% after 10 years.[6] It is a health problem with greater incidence in people between 30-60 years of age and more common in men than in women.[7]

The difference in prevalence between countries is associated with the combination of genetic and environmental factors, including dietary habits, climatic conditions and socio-economic status.[4] For example, several studies show that the incidence is higher in populations of warm countries compared to populations in cold countries. It has also been found that high consumption of salt, animal protein, calcium, fatty acids and sugar are risk factors for the development of kidney stones.[4,7] Finally, renal lithiasis has been associated with a family history of kidney stones and with some diseases such as diabetes, hypertension, hyperthyroidism, obesity, metabolic syndromes, gout and urinary tract infections.[4,8]

The stones may be composed of calcium phosphate, uric acid, struvite, cystine and oxalate calcium. The oxalate stone are the most frequent, being present in

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more than 80% of the uroliths.[8] For this reason, this study will focus on oxalate stones.

The mechanisms involved in the formation of calcific stones are not fully understood.[5] It is generally agreed that urinary lithiasis is a multifaceted biological process that involves physicochemical changes and supersaturation of urine[9] leading to crystal nucleation, aggregation and growth of insoluble particles.[10]

For the treatment of renal stones minimally invasive surgery is used, it's effectiveness to broke the calculi but it has not reduced recurrence rates.[7,10] On the other hand, many drugs have been used, such as, thiazide diuretics, potassium citrate, non-steroidal anti-inflammatory drugs (NSAIDs); but they're only used for prevent or treat the symptoms.[7,8,10]

For these reasons, many studies have been focused to understand the mechanism involved in the renal lithiasis and in the development the new drugs for the treatment and prevention of this pathology and its recurrences. Herein, in this paper, it is shown a review about formation of calcific stones, their treatment and the pharmacological models to study of the antilihtiatic activity in oxalate stone.

Formation of renal stones

The mechanisms involved in the formation of calcific stones are not fully understood.[5] Renal stone formation is a biological process that involves physicochemical changes and supersaturation of urine.[9] It is explained through of the loss of the equilibrium between promoters and inhibitors of the crystallization,[2] urine composition and renal morphoanatomy.[3]

Recently, the promoters and inhibitors of the urine has been referred as modulators, which can be small molecules or low-molecular weight that modify supersaturation of the urine by serving as chelators of calcium and oxalate by forming soluble complex. The formation of this complex depends on numerous physicochemical factors such as the concentration of individual (competing) chemical species, the relative magnitude of the formation constants of the complexes themselves, the pH and ionic strength of the urine in which the process occurs.[11] As a result of supersaturation, solutes precipitate in urine leads to nucleation and then crystal concretions are formed.[9]

The first step in the formation of kidney stone begins by the formation of nucleus (termed as nidus), normally of apatite (calcium phosphate) due to that the heterogeneous nucleation is easier than homogeneous nucleation in physiological conditions of the urine.[12] It is the transformation from a liquid to a solid phase in a supersaturated solution.[13] A widely held theory is that of Randall's plaques, which proposes that subepithelial interstitial calcium-based deposits act as nuclei for stone formation. These plaques originate adjacent to the thin limbs of loops of Henle as spherical particles, which could be related to the high local ion concentrations at this site, and can extended to the interstitium.[14-16] Recent studies have investigated the role of oxalate-degrading bacteria. These form apatite structures that serve as a crystallization center for the formation of stones and could be a pharmacological target to avoid the nucleation process. Also, existing epithelial cells, urinary casts, RBCs, and other crystals in urine too can act as nucleating centers in the process of nuclei formation termed as heterogeneous nucleation.[9]

The growth process is very important due to the small stones are expulsed by urine, but the big stones require medical treatment. Its mechanism is simple because only requires the addition of new particles of the urine.[12] This process can be favored by the retention of microcrystals in the urothelium and controlled by the lithogenesis inhibitors.[3,17] Recent studies have demonstrated that oxalate produce damage to renal cell by the generation of reactive oxygen species[18]; which increase the surface expression of phosphatidylserine, sialic acid, hyaluronan, osteopontin, or the glycoprotein receptor CD44, resulting in more crystal adhesion and formation of the nidus for the formation of stone.[5] On the other hand, the presence of renal cavities with low urodynamic efficacy retain urine by long periods of time in the upper urinary tract, which favors the formation of stone.[19] Finally, there are substances in the urine act as inhibitors of lithogenesis through of the inhibition in the crystal surface; also, there substances have complexing properties with some ions involved in the precipitation process decreasing its concentration.[12] Several inhibitors have been found in the urine as citrate, phytate, magnesium and pyrophosphate ions[3] and other molecules as uropontin, osteopontin, bikunin, and Tamm-Horsfall protein[15]; but citrate, magnesium and phytate have been the most studied.[19-20]

Treatment of renal stones

The treatment of the calculi will depend of their size and site, and of any symptoms and signs, particularly of obstruction. When the stones are less than 10 mm can be expulsed with pharmacologic treatment, but, when the calculi are higher than 10 mm or can't be expulsed with pharmacologic treatment, it is necessary to use of minimally invasive surgery,[8,14] such as extracorporeal shockwave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), or ureteroscopy (URS), which has revolutionized acute and complex stone management.[5] The problem

is that these techniques don't prevent the likelihood of new stone formation because often result in incomplete stone clearance.[5,10,18] Then, to reduce the rate of stone recurrence is necessary the intervention in the form of lifestyle advice and some forms of medical therapy.[5] For example, the increase of liquid, potassium, magnesium, calcium, vegetable and fruit intake and the decrease of sodium, animal protein and fat consumption has been associated with reduction of renal stone.[1,7,14,21,22] On the other hand, many drugs have been used to prevent the recidives, for example, thiazide diuretic, potassium citrate, allopurinol, NSAIDs, calcium antagonist, pirydoxine, alfa-blockers.[8,14,21,22] However, the scientific evidence about the efficacy of the pharmacologic therapy is less convincing.[10,17,23] All these facts indicate the need for new therapeutic approaches for the treatment of renal stones,[18] therefore, new alternatives are being tested using herbal medicine or phytotherapy.[17]

Traditional medicine in renal lithiasis: a therapeutic solution?

The use of medicinal plants dates from the beginnings of humanity, when people had no other effective therapeutic resources to treat their diseases. This knowledge was transmitted through legends, pictographs and various monographs until our days.[24] The oldest written evidence of medicinal plants' usage for preparation of drugs has been found on a Sumerian clay slab from Nagpur, approximately 5000 years old. Other ancient references were showed in «The Chinese book on roots and grasses» written by Emperor Shen Nung around 2500 BC, «The Indian holy books Vedas» and "The Ebers Papyrus", written about 1550 BC.[25]

According to data from the World Health Organization (WHO), 80% of the world's population uses plants as a remedy to cure their diseases.[26] On the other hand, it is known that around 20% -30% of the medicines available in the market are derived from natural products.[27]

Recently the use and commercialization of medicinal herbs has increased in developed and developing countries, linking several multinational companies, which have obtained benefits of up to $ 7.00 billion in Europe, $ 3.2 billion in the United States and $ 2.3 billion in Asia (Table 1). The reasons for this increase are due to the preference of consumers for natural therapies; concern regarding undesirable side effects of modern medicines and the belief that herbal drugs are free from side effects, since millions of people all over the world have been using herbal medicines for thousands of years; great interest in alternative medicines; preference of populations for preventive medicine due to increasing population age; the belief that herbal medicines might be of effective benefit in the treatment of certain diseases where conventional therapies and medicines have proven to be inadequate; tendency towards self-medication; improvement in quality, proof of efficacy and safety of herbal medicines and high cost of synthetic medicines.[28]

TABLE 1. Richness obtained from sales of herbal medicines in some countries in the year 1996.

Country	Incomes (USD)
Germany	$3.5 billion
United States of America	$3.2 billion
Japan	$2.1 billion
France	$1.8 billion
Italy	$700.0 million
United Kingdom	$400.0 million
Spain	$300.0 million
Netherlands	$100.0 million

The best acceptance of the population of herbal medicine, the wide traditional knowledge about medicinal plants, the few scientific studies that support the therapeutic properties of these and the interest of the pharmaceutical industry in the development of phytopharmaceuticals constitute opportunities in the research of herbal medicines as therapeutic alternatives for several diseases, especially in those in which conventional medicine has not been very effective. On the other hand, herbal medicines usually contain a range of pharmacologically active compounds. This could be an advantageous characteristic for the therapeutic application of herbal medicine, since sometimes beneficial synergisms are established in the treatment of some diseases, being able to be more effective than synthetic drugs.

As mentioned earlier, several researchers have focused their attention on herbal medicine for the treatment of renal lithiasis because, currently, this pathology is treated by minimal access surgery and pharmacological therapy is less convincing.

The traditional knowledge about medicinal plants is the first clinical evidence on efficacy of herbal medicine, however, scientific studies are necessary to corroborate the ethnobotanical information.[28] Recently, a list of antilithiatic plants used by population of different countries of the world was published, where already 500 species belonging to 106 families were identified. The families more representative in this study were Asteraceae (87), Fabaceae (71), Lamiaceae (58), Rubiaceae (17), Solanaceae (12), Phyllanthaceae (9), Zingiberaceae (9), Rutaceae (9), Polygonaceae (8) and Urticaceae (8).[29-31] Other reported families were Rosaceae (41), Poaceae (24), Malvaceae (23), Brassicaceae (20) and Boraginaceae (13).[32-33] The wide traditional knowledge of antilithiatic plants favors the researches of herbal medicine in this pathology because it increases the chances of finding an effective therapeutic treatment.

Cuban herbal medicine and renal lithiasis

In Cuba, the first evidence about the use of medicinal plants was found in the primitive community, where "el behíque" was the second most important person into the community. Among its functions was the treatment of patients through remedies made with medicinal plants.[34] On the other hand, in the wars of independence (XIX century), "los mambises" found in the Cuban flora a solution to the cure of their wounds and diseases. For example, José Martí mentioned in his Campaign Diary the benefits of "hijereta", "cilantro" honey and other remedies used in camps.[35] In 1945, the Cuban scientist Juan Tomás Roig published his book «Plantas Medicinales y Aromáticas de Cuba» where he described more than five thousand medicinal species used by the Cuban population.[36] Recently, the Ministry of Public Health of Cuba created the National Program of Natural and Traditional Medicine and elaborated the National Therapeutic Guide of Phytodrugs and beer-derived products for its application in health institutions.

The great variety of medicinal plants in the Cuban flora, together with the widely ethnobotanical knowledge increases the opportunities for the search of new therapies in the treatment of various diseases, of which, the renal affections have been one of the most treated in the ethnobotany. However, the phytotherapeutic potential of the island is still virgin. For example, in ethnobotanical studies made in Cuba, one hundred seventy-nine species have been used in the renal system, of which only 9% have been evaluated pharmacologically.[37-39] Table 2 shows a compilation of some plants used for the treatment of kidney stones according to ethnobotanical studies carried out in different areas of the country.

Bashir and Gilani (2009) demonstrated the antilithiatic activity of the methanol 30% extract from *Bergenia ligulata* using *in vitro* and *in vivo* studies. The extract showed capacity to evite the crystallization trough in vitro calcium oxalate crystallization test. Also, the capacity to decrease the renal damage produced by oxalate crystals through generation of Reactive Oxygen Species (ROS) was corroborated by DPPH assays. The diuretic activity and antilithiatic activity of the extract was demonstrated in Wistar rats.[44] After that, the authors evaluate the antilithiatic activity of Berberine, an alkaloid described for this plant, and they obtain similar results to the methanol 30% extract.[10] A similar study was done in *Selaginella lepidophylla*, but, in this case the antilithiatic activity was related with the presence of polyphenols and flavonoids in the plant.[17] The antilithiatic effect of other medicinal plants used by population, such as, *Costus spiralis, Phyllanthus niruri, Origanum vulgare, Hibiscus sabdariffa, Zea mays*[10,45], *Berberis trifoliata*[46], *Punica granatum*[23] *and Terminalia arjuna*[5] has been demonstrated with promisorius results. Generally, this effect has been attributed to polyphenols[47] and flavonoids.[48]

The ethnobotanical use and the scientific evidence about the mechanism of action and related chemical compound with antilithiatic activity is a proof of the effectiveness of the medicinal plant in the treatment of this pathology, however, the controlled clinical trials are required. Then, future studies should be leaded in this way.

TABLE 2. Herbal medicine used by Cuban population to treat the lithiasis renal.

Plant	Family	Commun name	Part(s)	Preparation	Ref.
Blechum pyramidatum	*Acanthaceae*	Mazorquilla	Aerial	Decoction	[39]
Caesalpinia bahamensis	*Caesalpinaceae*	Brasilete	Stem	Decoction	[40]
Chiococca alba	*Rubiaceae*	Bejuco verraco	Root	Decoction	[41]
Cymbopogon citratus	*Poaceae*	Caña de limón	Stem	Decoction	[40]
Cyperus rotundus	*Cyperaceae*	Caramamá	Root	Decoction	[41]
Erythroxylum havanense	*Erythroxylaceae*	Jibá	Root	Decoction	[41]
Guazuma ulmifolia	*Sterculiaceae*	Guásima	Bark	Decoction	[41]
Heliotropium angiospermum	*Boraginaceae*	Alacrancillo	Leaves	Infusion	[40]
Lepidium virginicum	*Brassicaceae*	Matuerzo	Leaves	Decoction	[42]
Lonchocarpus pentaphyllus	*Fabaceae*	Guamá amarillo	Stem, Root	Decoction	[39]
Momordica charantia	*Cucurbitaceae*	Cundeamor	Leaves	Infusion	[40]
Peperomia pellucida	*Piperaceae*	Corazón de Hombre	Aerial	Decoction	[41]
Polypodium polipodiodes	*Polypodiaceae*	Doradilla	Leaves	Decoction	[39]
Rystonea regia	*Arecaceae*	Palma real	Root	Decoction	[40]
Salpianthum purpurascens	*Bignoniaceae*	Nitro	Aerial	Decoction	[40]
Trichilia glabra	*Meliaceae*	Siguaraya	Leaves	Infusion	[40]
Urera baccifera	*Urticaceae*	Chichicate	Root	Decoction	[40]
Xanthium strumarium	*Asteraceae*	Guizaso de caballo	Root	Decoction	[40]
Xiphidium coerelum	*Haemodoraceae*	Cola de paloma	Leaves	Infusion	[43]
Zea mays	*Poaceae*	Maíz	Hair	Infusion	[40]

DISCUSSION

Renal lithiasis is an important global renal problem due to its high incidence and the lack of effective pharmacological treatments. Until now, the minimally invasive surgery is the only option to destroy the renal calculi. Then, the search for new therapeutic alternatives continues being a topic of interest in the scientific community, where medicinal plants have gained an important place on research in this field. Despite the widespread use of plants in traditional medicine, their therapeutic application is limited due to the lack of scientific studies that support their therapeutic properties, especially clinical studies.[28] However, a study done by Newman & Cragg, (2016) shows that 50% of the drugs approved in the period 1981 to 2014 originated in natural products.[49] This evidence shows that plants are an effective resource for the treatment of diseases, however, studies that support their use in therapeutics are required, which is one of the weaknesses in the clinical application of herbal medicine. On the other hand, several *in vitro, in vivo* and clinical studies have been developed in plants traditionally used for the treatment of renal lithiasis with promising results, however, the phytochemical studies of the plants have been insufficient. As a consequence, the validity of the studies is limited because without

phytochemical characterization, quality control is difficult and reproducibility of results questionable. The available information shows that some possible mechanisms of action of plant extracts include an increased excretion of urinary citrate, decreased excretion of urinary calcium and oxalate, ability to inhibit the crystallization process of oxalate calcium or could be attributable to diuretic, antioxidant or antibacterial effects.[50]

Summarizing, the best acceptance of natural products in the world population, the interest of the pharmaceutical industry in the development of these, the traditional knowledge of a great variety of plants for the treatment of lithiasis and the promising results of the scientific studies carried out are elements that support the theory that plants could be an effective therapeutic resource for the treatment of renal lithiasis, however, still requires phytochemical and biological studies that reinforce this theory.

CONCLUSION

The higher incidence and prevalence of renal lithiasis and the lack of an effective pharmacological therapy for its treatment are focused of attention for several researchers in the development of new drugs, being the natural products a potential source of bioactive molecules for this pathology.

Conflict of Interest: The authors declare not conflict of interests.

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