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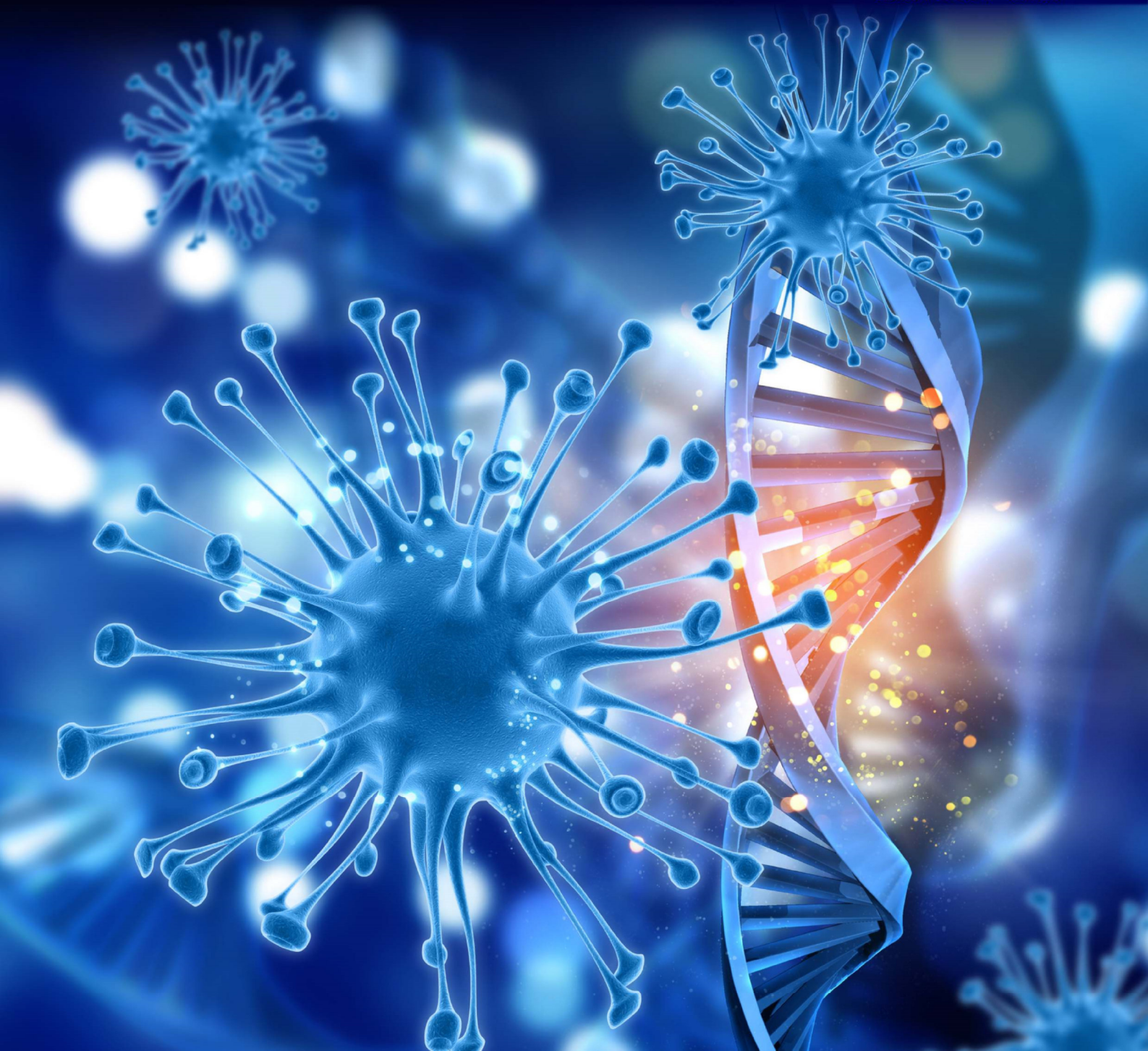

JOURNAL OF
SOUTHEAST ASIAN
MEDICAL RESEARCH

Introduction

The Journal of Southeast Asian Medical Research is a peer-reviewed journal with printing every 6 months. The main goal of this collaboration project is to distribute new knowledge in medical sciences to medical communities and scientists, as well as encouraging scientific collaborations within Southeast Asia and also other nations around the world. The journal publishes original research in the medical sciences: clinical and basic. We welcome original articles from across the world. The editorial board comprise of international experts in various fields of medicine, ranging from internal medicine to a variety of surgeries. The full text of the journal is available online at http://www.jseamed.org

It is our aim to publish the most up-to-date and useful research information in medical sciences. In Southeast Asia, there are some unique problems in health care and diseases, such as tropical diseases, and it is crucial that health professionals can access, share and exchange knowledge promptly. In this region, there is still a gap of knowledge in health sciences that needs to be closed by scientific research, which we are hoping to close after this collaboration project. We hope that the journal will fulfill the objectives and will provide benefit to all, both medical practitioners and researchers alike.

Editorial board

JOURNAL OF SOUTHEAST ASIAN MEDICAL RESEARCH

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EFFICACY OF WEEKLY INTRA-ARTICULAR LOW MOLECULAR SODIUM HYALUTONATE INJECTION FOR THREE WEEKS IN THE TREATMENT OF OSTEOARTHRITIS: OPEN RANDOMIZED CLINICAL TRIAL

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Abstract

The primary objective of this study was to determine whether the three-weekly injections improve knee pain and patients' quality of life. The secondary objective was to assess patients' compliance to treatment and risks related to the three-weekly injections of Hyalgan®. The authors conducted a single-blind randomized controlled trial. Osteoarthritis knee participants aged 50 years or older with early osteoarthritis knee or Kellgren-Lawrence grade I to III were randomized to intra-articular injection of three-weekly doses (the intervention group; n = 50) or five-weekly doses of Hyalgan® (the control group; n = 50). The outcomes of the study were measured at baseline, 1, 2, 3, 4, 5, and 8 weeks post-treatment. The weight-bearing after 50 foot-walking and patients' quality of life at the baseline measured by visual analog scale(VAS) and Thai short form 36 (SF-36) health survey score were not significantly different between the two groups (p = 0.430 and 0.239, respectively). The VAS was statistically lower at the 1st and 2nd week in the three-weekly intra-articular injections group (p = 0.009 and 0.005, respectively). The evaluation of overall changes in the Thai SF-36 score also revealed that patients in the three weekly injection group had a higher quality of life compared to the other group (p = 0.0001). The numbers of loss to follow-up in the intervention group were significantly lower than the control group (2 cases vs. 7 cases, $p < 0.05$) . And no complication related to intra-articular injection was found in the two treatment groups. In conclusion, the results of this present study support the hypothesized superiority of managing pain associated with knee OA and increasing patients' quality of life in the three weekly injections over the conservative management of the five weekly injections. More importantly, the safety of the treatment has been warranted.

Keywords : Osteoarthritis knee, Hyaluronic acid, Viscosupplementation, visual analog scale, Thai short form 36 health survey score

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Introduction

Sodium hyaluronate is the main component of joint fluid and cartilage.[1-3] Knee arthritis causes a reduction in its concentration which results in chronic knee pain[4]. There is evidence that the supplementation of exogenous sodium hyaluronate can alleviate the pain by restoring the viscoelastic properties of the synovial fluid and stimulates synoviocytes to synthesize endogenous hyaluronic acid.[5-7]

Low-molecular weight viscosupplementation has been widely used for the treatment of early osteoarthritis knee (OA) (classification based on Kellgren-Lawrence grade I-III)[8]. Patients treated with the supplement benefit from the long-term safety and decreased risk of adverse serious gastrointestinal effects, the complications from prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs).[9-12] A five-weekly injection of sodium hyaluronate has shown to be effective for pain relief in this group of patients.[12, 13] It is global standard practice to provide the five-weekly injections in patients diagnosed with knee osteoarthritis. However, there are some drawbacks from the course of treatment. For example, the whole course is relatively long for the duration. The intra-articular knee injection itself is considered to be painful, and patients are also exposed to a chance of intra-articular bleeding and infection or pseudo-septic reactions knee.[14]

To avoid these complications and shorten the length of treatment, management with appropriate numbers of injection course should be proposed. As such, the authors designed a randomized controlled trial (RCT) comparing efficacy and effectiveness between a shorter of three-injection course and the standard course. The primary objective of this trial was to determine whether the three-weekly injections improve clinical outcomes of patients. Our primary hypothesis was that treatment with the three-weekly injections would result in reduced weight-bearing pain after 50-foot walking as well as an improvement in patient quality of life at eight weeks. Our secondary outcome was that incorporating the three-weekly injections into the management of knee osteoarthritis would enhance patients' compliance to treatment without increasing risk of septic or pseudo-septic reactions.

Patients and methods

The study was a two-arm RCT with randomized assignment to intra-articular injection of three-weekly doses (the intervention group) or five-weekly doses of Hyalgan® (the control group). The study was started at Buddhachinaraj Phitsanulok Hospital; between July 1, 2016, and June 30, 2017. The study was approved by the Research and Ethics committee at the study center (IRB reference number: 030/59). The sample size was calculated based on whether there is a difference in the efficacy of the three-weekly doses injection and five-weekly doses (hypothesis testing of an equivalence trial). The α was set at 0.05, and β at 0.2 to determine a standard deviation (σ) of 10 as well as the clinically acceptable margin of the outcome of 7. The total expected sample size was 48 cases per arm with an additianal of 2 cases assigned to each group to compensate any attrition along the follow-up period.

All patients presenting with knee osteoarthritis were screened for eligibility on their first visit at the study hospital. To be included in the study, patients had to be 50 years of age or older and have early osteoarthritis knee or a grade on the Kellgren-Lawrence (KL) of I to III. (The Kellgren-Lawrence ranges from grade 0 to IV, with higher grade indicating more severe of knee osteoarthritis[8]). Patients with a history of allergy to Hyaluronic acid, severe degenerative spine, severe Genu Varus and Genu Valgus; as well as those with septic arthritis, inflammatory arthritis, and previous use of intra-articular steroid within six months were excluded from the study. The information on screening, randomization, and follow-up was presented in **Figure 1**. Informed consent was obtained for all participants.

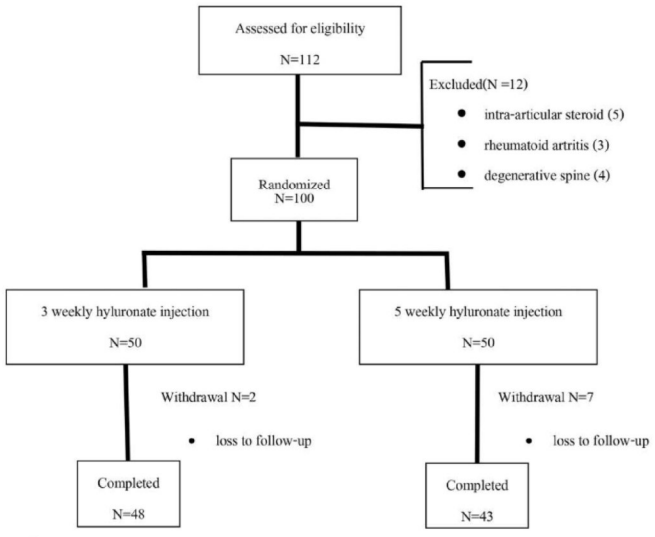

Fig 1. Patient Distribution

A simple random sample was performed to assign patients to the intervention group and the control group. A list of eligible patients on their first visit was obtained from a screening nurse every day during the study period. Each patient was marked with a specific number (1 and 2). Patients with number 1 were assigned to the intervention group and 2 to the control group, respectively. Patients in the intervention group received three- weekly intra-articular injections of Hyalgan® (4 ml dose at the 1st and 2nd week follow by 2 ml dose at the 3rd week). The control group obtained a 2 ml-weekly dose for the consecutive five weeks. Sodium Hyaluronate or Hyalgan® 500 – 730 kilodalton (kDa) is the Food and Drug Administration (FDA) approved the drug for the treatment of osteoarthritis of the knee joint since May 1997 and have been used extensively in Thailand.

To eliminate confounding factor causing by investigators' expectations, a single-blind technique was established. During the procedure, each patient was asked to lie on an examination table in the supine position with their knees extended; then the injection site was marked along the superolateral corner of the patella.[15] A well-trained orthopedic surgeon was the only person who performed the intra-articular injection procedures for all participants. Acetaminophen was a sole pain reliever provided after the procedure. Participant demographic and clinical characteristics, for example, age, gender, body mass index (BMI), side of affected knees, signs and symptoms at first visit, and KL grade were documented. The primary outcome was a composite of two components: measures of the weight-bearing after 50 foot-walking (visual analog scale of 0 – 10 cm.) and patients' quality of life (Thai SF-36 health survey score)[16-17]. For the secondary outcome, patients' compliance to treatment measured by follow-up rates and the occurrences of complication from the intra-articular injection (e.g., septic or pseudo-septic reactions knee) were recorded[18,19]. Trained examiners who were unaware of the group assignments administered the tests at the baseline, 1st, 2nd, 3rd, 4th, 5th, and 8th week.

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 17.0. Descriptive statistics were calculated for the patient demographic and clinical characteristics. Differences in data were tested using Chi-square tests for categorical variables and one-way ANOVA for continuous variables. A two-sided significance level of 0.05 was used to test both primary and secondary hypotheses.

Results

Patients were recruited between July 1, 2016, and June 30, 2017 (see **Fig. 1** for information on screening, randomi zation, and follow-up). Of 112 eligible patients, 12 (11%) were excluded before randomization. Five patients received intra-articular steroid within six months before the recruitment; three had rheumatoid arthritis, and four had a severely degenerative spine. Of patients who underwent randomization, 91% were followed for eight weeks. Two patients from the intervention group were lost to follow-up, and seven were from the control group. None of them had a complication related to intra-articular injection. Of the study participants who underwent randomization, patients in the three-weekly injections group had a BMI that was statistically higher than another group ($p < 0.05$) with the mean BMI of 27.2 (SD± 4.33) compared to 24.89 (SD ± 3.73). There were no statistically significant differences in age, gender, or concerning pre-treatment symptoms. The weight-bearing after 50 foot-walking and patients' quality of life at the baseline measured by visual analog scale (VAS) and Thai SF-36 health survey score were not significantly different between the two groups ($p = 0.430$ and 0.239, respectively). **Table 1** shows a comparison of the baseline characteristics of enrolled patients.

Table 1. Patient baseline characteristics by study group

Baseline characteristics	3 weekly injections (N=50)	5 weekly injections (N=50)	*p*- value
Age (years)	65.16 ± 7.45	65.24 ± 8.78	0.961
Gender			1.0
Female	13	14	
Male	37	36	
BMI	27.2 ± 4.33	24.89 ± 3.73	0.005
Diagnosis Osteoarthritis (years)	4.54 ± 6.23	3.27 ± 3.95	0.484
Position			0.419
Right knee	22	27	0.419
			0.369
Left knee	28	23	0.419
Kellgren-Lawrence grade			0.369
I	10	5	0.369
			0.213
II	36	41	0.369
III	4	4	0.213
Sign & Symptoms			0.213
Pain	50	50	0.430
Swelling	4	2	0.213
VAS	5.62 ± 2.07	5.92 ± 1.70	0.430
SF-36	416.6±121.6	414.6±130.1	0.239

Data were tested by Chi-square tests

* statistically significant ($p < 0.05$)

The authors determined the efficacy of the study intervention and found that the VAS after a 50-foot walk in both groups decreased significantly between the 1st and 8th weeks (p <0.05). The VAS was statistically lower at the 1st and 2nd weeks in the three weekly intra-articular injections group (p = 0.009 and 0.005, respectively). The results for the VAS after the 50-foot walk in both groups are shown in **Table 2**. The trends of mean VAS scores after the 50-foot walk are illustrated in **Figure 2**.

Table 2. Patients' Visual analog scale after 50-foot walking (VAS) evaluation after treatment with 3th and 5th weekly intra-articular sodium hyaluronate

	VAS		
Week	3 weekly injections (N=50)	5 weekly injections (N=50)	p- value
0	5.62 ± 2.07	5.92 ± 1.7	0.430
1	3.88 ± 1.76	4.88 ± 1.90	0.009*
2	3.14 ± 1.51	4.08 ± 1.74	0.005*
3	3.06 ± 1.77	3.5 ± 1.46	0.189
4	2.88 ± 1.61	3.04 ± 1.38	0.588
5	2.63 ± 1.72	2.59 ± 1.55	0.921
8	2.38 ± 1.65	2.37 ± 1.65	0.993
average	3.38 ± 2.00	3.83 ± 2.03	0.004*

Data were tested by one-way ANOVA

* statistically significant (p < 0.05)

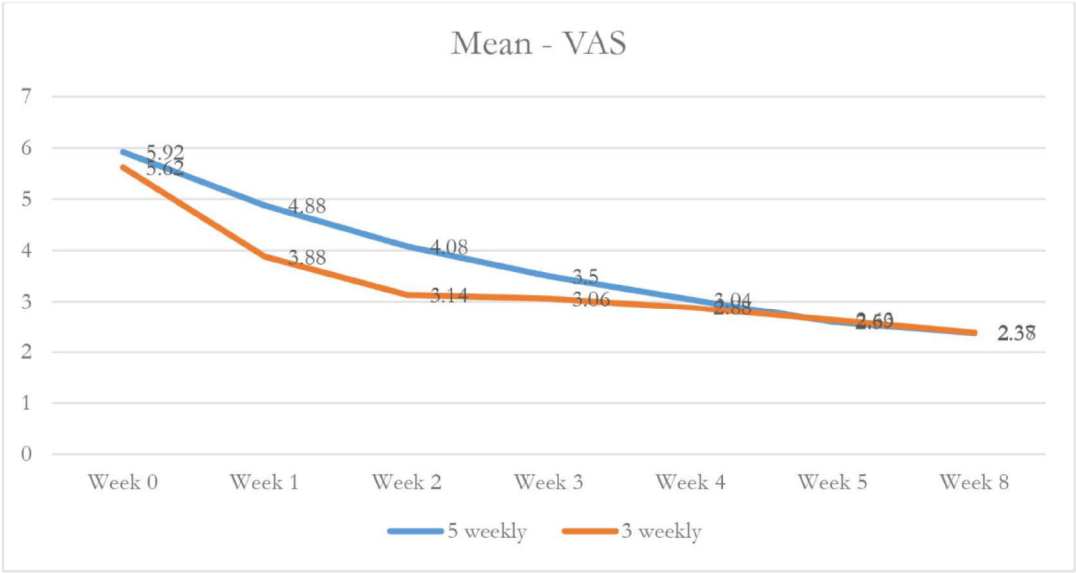

Fig 2. Patients' mean Visual analog scale after 50-foot walking (VAS) evaluation after treatment with 3th and 5th weekly intra-articular sodium hyaluronate.

The results from a week-by-week analysis of patients' quality of life measured by Thai SF-36 score were similar for both groups (p >0.05) (**Table 3**). However, the changes in the Thai SF-36 score between pre- and posttreatment were statistically significant (p <0.05). The evaluation of overall changes in Thai SF-36 score also revealed that patients in the three weekly injection group had a higher quality of life compared with the other group (p = 0.001). **Figure 3** demonstrates changes in patients' quality of life over the eight weeks of the study.

Table 3. Patients' Thai SF-36 health survey score evaluation after treatments with 3 and 5-weekly intra-articular sodium hyaluronate

Week	Total SF-36		p-value
	3 weekly injections (N=50)	5 weekly injections (N=50)	
0	51.8±16.3	52.1±15.2	0.239
1	53.9±15.9	57.4±16.2	0.107
2	55.4±16.8	58.7±16.2	0.106
3	58.2±17.1	59.2±16.7	0.148
4	60±17.8	59.3±17.5	0.208
5	60.3±17.6	59.8±16.9	0.114
8	60.7±17.5	60.5±15.8	0.202
average			0.0001*

data were tested by one-way ANOVA

* statistically significant (p < 0.05)

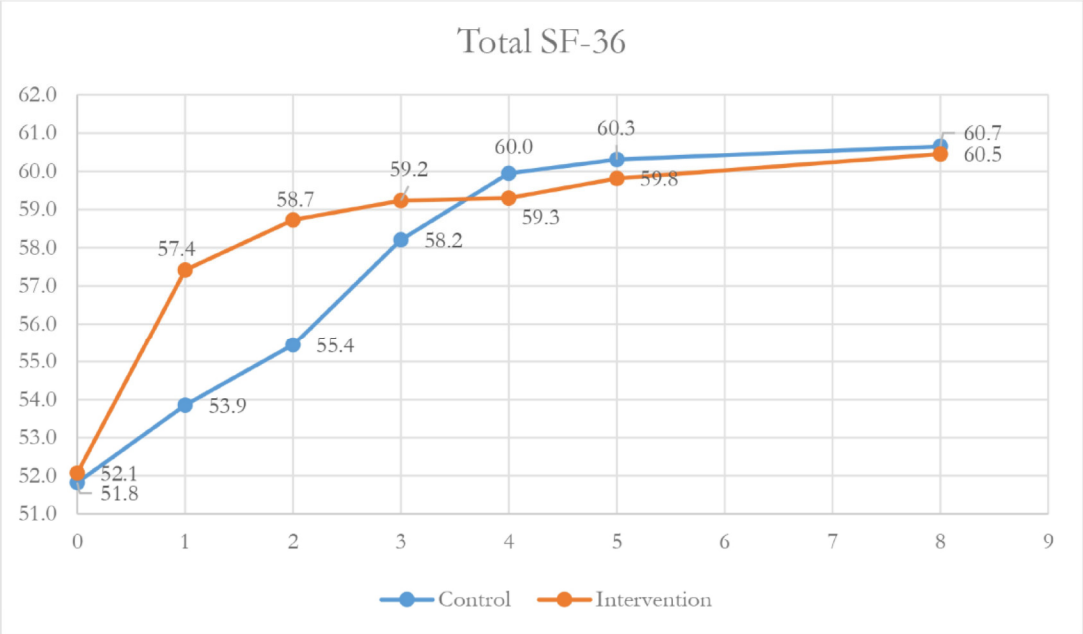

Fig 3. Patients' Thai SF-36 health survey score evaluation after treatment with 3 and 5- weekly intra-articular Sodium hyaluronate

Our secondary hypothesis examined whether incorporating the three weekly injections course in the management of knee OA would improve patients' compliance to treatment without increasing risk of septic or pseudo-septic reactions knee. The authors found that the numbers lost to follow-up in the intervention group were significantly lower than in the control group (2 cases vs. 7 cases, p <0.05) (**Figure 4**). No complication, related to intra-articular injection, was found in the two treatment groups.

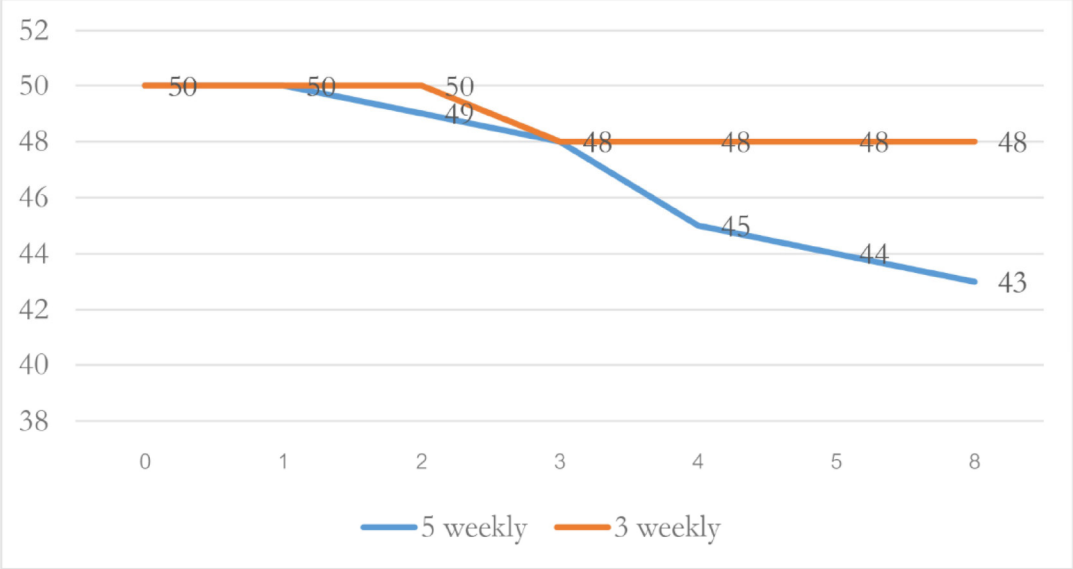

Fig 4. Number of patients after treatment with 3 and 5-weekly intra-articular Sodium hyaluronate

Discussion

OA is a chronic disease that involves cartilage degradation, bone remodeling and bone overgrowth. Patients with OA usually suffer from pain and long term disability. To date, pharmacologic treatments including analgesics and NSAIDs are recommended along with various nonpharmacologic modalities such as exercise and weight reduction. [5-7, 9-13]

However, most currently available pharmacologic treatment has its own limitations regarding tolerability and durability. Long term use of NSAIDs can cause serious complications consisting of upper gastrointestinal bleeding and renal failure. As an alternative, the potential benefit of intra-articular injection of low molecular weight hyaluronic acid in alleviating pain associated with OA is of increasing interest. Many studies have investigated the efficacy and safety of intra-articular hyaluronic acid, especially for knee OA. The compiled available evidence suggests a positive effect of this drug in reducing pain and improving function.[12]

In Thailand, the standard practice provides a five weekly injection course of hyaluronic acid among patients diagnosed with knee OA. However, the long duration of treatment is more likely to expose patients to a chance of intra-articular bleeding and infection or pseudo-septic knee reactions.[14] To investigate the benefit of a shortened course of intra-articular hyaluronic acid injection; the authors gathered qualitative data from a randomized, single-blind comparative study to determine the efficacy and effectiveness of the three weekly injections compared with those of five weekly injections.

The results of this present study supported the hypothesized superiority of managing pain associated with knee OA and increasing patients' quality of life in the three weekly injections over the conservative management of the five weekly injections. As has been noted in the study, the onset of knee pain relief following hyaluronic acid treatment in the three-weekly-injection group was rapid and apparent within the 1st and 2nd week of starting treatment. It also demonstrated significantly superior results in controlling pain and improving patients'

quality of life over the eight-week duration. More importantly, the safety of the treatment has been justified because the participants did not report any signs of complications related to the intra-articular injections. In addition, a higher rate of patients' compliance to treatment was demonstrated in the intervention group.

In comparison with the earlier trials, reports have shown that the three weekly intra-articular injections of Hyalgan® and the five weekly injection did not exhibit any significant difference in pain relief among patients with knee OA.[20] In our study, the authors increased Hyalgan® from a 2 ml to a 4 ml dose. The higher viscosity improved the visco-elastic properties of synovial fluid and alleviated pain a more effectively. However, both present and related studies showed a concordant result pertaining to significant pain relief after five weeks of hyaluronic acid treatment.

Notably, this study evaluated the short term outcomes of intra-articular hyaluronic acid treatment. Thus, it should not be compared with studies that investigated long term outcomes of such treatment. The authors declare they have no conflict of interest regarding the publication of this article. The randomized controlled trial is appropriate as an optimal method to establish the efficacy of a new intervention compared with the control treatment. Nonetheless, in this study, important limitations were observ ed regarding its relatively short observation period as well as the high attrition of eligible participants. These limitations might have introduced bias in the study's results. We suggest a future study to develop a management approach to prevent losses from follow-up and enhance patient adherence, especially for those with chronic diseases like OA. The approach includes ensuring good communication between study staff and participants, accessibility to the clinic, effective communication channels, incentives to continue and ensuring that the study is of relevance to the participants.

Conclusion

In conclusion, this trial shows that the three weekly injections of Hyalgan® were effective over eight weeks. Additionally, is the treatment was also superior to the five weekly injections regarding reducing VAS pain, increasing quality of life, improving patients' compliance to treatment and the safety of the treatment has been justified. However, this present study only examined short term outcomes in a small sample size. Further studies to elucidate long -term effects of three weekly injections in a larger number of patients should be conducted.

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STUDY OF THE GLYCEMIC INDEX OF THE MEDICAL FOOD NEO-MUNE

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Abstract

Objective: The study aimed to examine the glycemic index of the medical food Neo-Mune.

Methods: Ten healthy volunteers with normal pancreatic function were enrolled in this pilot study. All eligible subjects were asked to return to the research center a week later to consume 50 grams of glucose solution and their plasma glucose levels were measured at 0 (baseline), 30, 60, 90 and 120 minutes after glucose consumption. A week after that, the same cohort consumed 94.97 g Neo-Mune (advised carbohydrate provision of 50 grams) and again, their plasma glucose levels were recorded at 0, 30, 60, 90 and 120 minutes after consumption. The glycemic index (GI) was calculated from the area under the glucose response curve of Neo-Mune divided by the area under the glucose response curve of the glucose solution, multiplied by 100.

Results: The plasma glucose levels reached their highest levels at 30 minutes post-consumption and decreased gradually in both cases. However, the plasma glucose levels were lower at 30 and 60 minutes after Neo-Mune consumption compared with those after glucose solution consumption. The GI of Neo-Mune was identified as 42.12, which is classifies it as a low-GI food.

Conclusion: Neo-Mune, a low-GI food, is expected to show a low postprandial glycemic excursion after consumption.

Keywords : glycemic index; Neo-Mune; glycemic control

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Introduction

Currently, diseases related to excess calorie intake or maintaining a high fat or high sugar diet are increasing. These include diabetes mellitus (DM), dyslipidemia and cardiovascular diseases. Therefore, consumers are being encouraged to focus on healthy diets and lifestyle modification. One of the strategies being used is to control carbohydrate consumption, a main source of energy, to lower postprandial glycemic response. Carbohydrates are classified in 2 main groups: simple and complex carbohydrates. They differ in terms of glucose absorption and postprandial glucose excursion. The consumption of appropriate levels of carbohydrates is effective in controlling both spikes and baseline levels of plasma glucose.

The classification of food based on glycemic response or "glycemic index" (GI) has been found to be useful for both patients and medical teams in maintaining plasma glucose levels. The GI is the area under the plasma glucose response curve for each food consumed expressed as a percentage of the area under the plasma glucose response curve after taking the same amount of carbohydrate as a reference food, which is typically glucose or white bread. A 50 gram (g) glucose intake typically has a glycemic index of 100.[1] Different carbohydrate sources raise blood glucose differently. The GI measurement was originally designed for patients with diabetes as a guide for food selection. Low-GI food has a low glycemic response following ingestion compared with high-GI food, therefore low-GI food is appropriate for diabetic control to prevent or delay long term diabetic complications.[2] The GI classification is categorized as low- GI (GI less than 55), medium-GI (GI from 55 to 69) and high-GI (GI more than 70).[2]

The amount of food consumed is also a major determinant in postprandial glucose excursion. The concept of glycemic load (GL) takes into account the GI of food and the amount consumed.[3] The present study was designed to examine the glycemic index of Neo-Mune, an immunonutrition product. Neo-Mune is aimed at supporting immunocompromised patients; however, its impact on the glycemic response among vulnerable patients is a concern. This study intended to investigate this impact.

Methods

Study subjects

This study was approved by the ethics committee of the Faculty of Medicine, Chiang Mai University and conducted at the Clinical Trial Unit, Faculty of Medicine, Chiang Mai University. Ten eligible subjects signed consent forms and fulfilled the following criteria: were 18 years or older, had a body mass index (BMI) 18.5-24.9 kg/m^2, had no underlying diseases, had no history of DM in their families or had no history of allergy to any of the ingredients in the formula (cow's milk protein, glutamine, arginine, fish oil etc.). These subjects also did not meet any of the following exclusion criteria: had underlying diseases (including DM, hypertension, cardiovascular diseases, renal or liver disease, metabolic disease, thyroid disease etc.), had taken any medication or food supplement or any vitamins within 7 days before commencement of the study, were pregnant or lactating, or did not comply with the study protocol.

Study product

Neo-Mune, an immuno-enhancing formula, provides a caloric distribution consisting of approximately 50% carbohydrate, 25% fat and 25% protein (**Table 1**).

Table 1. Neo-Mune composition

Composition	In grams	Amount (g)	Calories (kcal)
Protein	Sodium caseinate	18.25	
	Glutamine	2.61	
	Arginine	5.21	
	Total	26.07	104.3
Carbohydrate	Maltodextrin	42.44	
	Trehalose	1.00	
	Fructose	5.21	
	Polydextrose	4.00	
	Total	52.65	210.6
Fat	MCT oil (52%)	6.28	
	Fish oil (19%)	2.32	
	Corn oil (29%)	3.48	
	Total	12.08	108.7
Total energy in 100.00 gram			423.6

Sample size calculation

Ten healthy subjects were enrolled in this pilot study. This was deemed to be the lowest sample size necessary to study the GI of the food.

Ethical aspects

The Research Ethics Committee, Faculty of Medicine, Chiang Mai University (No. 336/2016) approved the study design described below. All participants had to provide written informed consent before entering the study.

Study design and procedure

On screening days, the subjects had to abstain from consuming food and beverages for at least 10 hours. The subjects were informed about the study method and procedures before signing the consent form. The screening process involved a medical history check, a physical examination and laboratory tests for fasting plasma glucose, liver function, renal function, thyroid function, pancreatic function and a urine pregnancy test to confirm all inclusion and exclusion criteria. An oral glucose tolerance test (OGTT) was performed to evaluate pancreatic function. This was conducted by consuming a glucose solution which contained 75 g glucose dissolved in 250-300 mL of water within a 5-minute period. During OGTT, subjects were asked to remain still and not to smoke or drink any foods or beverages for 2 hours when their plasma glucose levels were measured. Those who had a 2-hour post-OGTT plasma glucose level of less than 140 mg/dL and other normal lab results were included in the study which was performed within 7±2 days.

At experimental visit 1 (Day 7±2), subjects had to abstain from consuming any food or beverages for at least 10 hours to evaluate their plasma glucose response after consuming a glucose solution containing 50 g of glucose dissolved in 400 mL of water within 5 minutes. Blood collection of 3 mL was drawn at 0, 30, 60, 90 and 120 minutes (on a normal saline solution (NSS) lock for convenience) after consumption.

At experimental visit 2 (Day 14±2), the subjects repeated the process of visit 1 (Day 7±2), the only difference being the consumption within 5 minutes of 94.97 g of Neo-Mune (providing 50 g of carbohydrate) dissolved in 400 mL

of water instead of the glucose solution. A second set of blood samples was used to measure plasma glucose levels. The plasma glucose levels after consuming the glucose solution and Neo-Mune were compared at each time interval. The GI of Neo-Mune was calculated as the area under the glucose response curve (AUC) within 2 hours after consuming Neo-Mune divided by the AUC within 2 hours after consuming the glucose solution and multiplied by 100. The GI recorded was the average GI from all 10 subjects.

Any adverse events that occurred during the study were addressed as open-ended questions and answers were recorded.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) when data was continuous data. Categorical variables were expressed as proportions (percentages). To compare all the continuous parameters in each patient between baseline and at 30, 60, 90 and 120 minutes, statistical significance was tested using repeated measure ANOVA tests. Categorical variables were compared using Fisher's exact test. All statistical tests were two-tailed and statistical significance was set at a *p*-value less than 0.05.

Results

Ten healthy volunteers were included with a mean age of 33.4 ± 5.2 years, mean body weight of 56.5 ± 9.1 kg, mean BMI of 21.1±1.9 kg/m2, mean fasting plasma glucose of 84.7 ± 9.9 mg/dL, mean systolic blood pressure (SBP) of 115.78 ± 10 mmHg and mean diastolic blood pressure of 73.1 ±8.7 mmHg. (**Table 2**)

Table 2. Baseline characteristics of 10 subjects

Variables	**Mean±SD**
Age (years)	33.4 ± 5.2 (26-42)
Weight (kg.)	56.54 ± 9.07
BMI (kg/m^2)	21.12 ± 1.93
SBP (mmHg)	115.7 ± 10.0
DBP(mmHg)	73.1 ± 8.7
Laboratory blood tests	
Plasma glucose (mg/dL)	84.7 ± 9.9
Total bilirulin (mg/dL)	0.66 ± 0.35
Direct bilirulin (mg/dL)	0.23 ± 0.09
Albumin (g/dL)	4.64 ± 0.24
SGOT (IU/L)	18.2 ± 5.09
SGPT (IU/L)	18.6 ± 12.88
Creatinine (mg/dL)	0.87 ± 0.26
BUN (mg/dL)	11.2 ± 1.75
TSH (mU/L)	1.48 ± 0.92

All 10 subjects had normal pancreatic function confirmed by the OGTT with a mean plasma glucose level of 97.7 26.3 (ranging from 53-138) mg/dL.

Plasma glucose reached its highest levels after 30 minutes in both postglucose solution and postNeo-Mune consumption before gradually decreasing. However, the plasma glucose levels at 30 and 60 minutes post Neo-Mune consumption were lower than the levels postglucose solution consumption; p = 0.004 and 0.005, respectively (**Table 3**). The incremental rise of plasma glucose levels from the baseline was also lower after Neo-Mune consumption than after glucose solution consumption at 30 and 60 minutes after consumption (**Figure 1**).

Table 3. Plasma glucose levels at each time after glucose and Neo-Mune consumption

Time after consumption (minutes)	Plasma glucose level (glucose solution) (mg/dL)	Plasma glucose level (Neo-Mune) (mg/dL)	Mean Difference (95%CI) (mg/dL)	p-value (mg/dL)
0	84.3 ± 8.27	77.4 ± 8.46	6.9 (-2.29, 16.09)	0.124
30	135.8 ± 29.64	110 ± 26.03	25.8 (10.71, 40.89)	0.004*
60	121.9 ± 28.12	89.3 ± 18.49	32.6 (12.76, 52.44)	0.005*
90	108.8 ± 25.75	94 ± 18.02	14.8 (-4.34, 33.94)	0.114
120	95.3 ± 25.51	83.4 ± 18.66	11.9 (-6.16, 29.96)	0.170

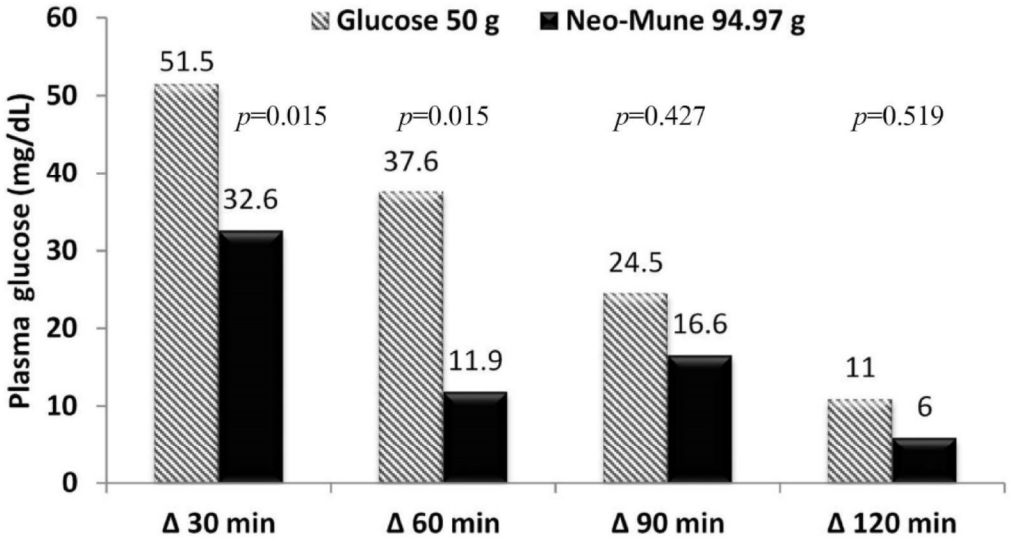
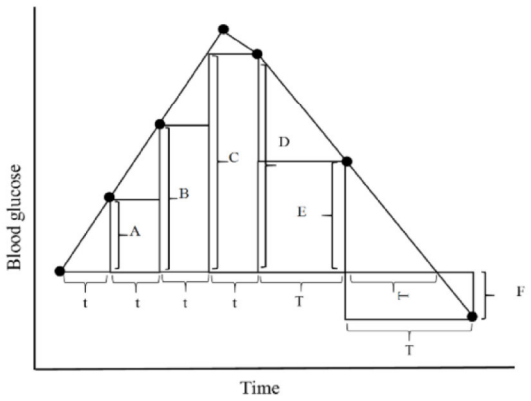


Fig 1. The incremental levels of plasma glucose from baseline at each time point after consuming glucose solution or Neo-Mune (mg/dL)

The GI was calculated based on the area under the plasma glucose response curve above the fasting levels only. The formula is shown in **Figure 2**[4] and the calculation was based on the data of the increments of plasma glucose values from baseline at each time point after consumption of the 50g glucose solution and 94.97g of Neo-Mune (**Table 4**)



$$Area = (A + B + C + \frac{D}{2})t + \frac{(D+E)T}{2} + \frac{E^2T}{2(E+F)}$$

Fig 2: Formulation and graph to calculate the area under the glucose curve4

Table 4. Calculations of incremental area under the plasma glucose response curve

Time (minutes)	Plasma glucose (glucose solution) (mg/dL)	Increment of plasma glucose level from baseline (glucose solution) (mg/dL)	Plasma glucose (Neo-Mune) (mg/dL)	Increment of plasma glucose level from baseline (Neo-Mune) (mg/dL)
0	84.3	-	77.4	-
30	135.8	51.5	110.0	32.6
60	121.9	37.6	89.3	11.9
90	108.8	24.5	94.0	16.6
120	95.3	11.0	83.4	6.0

Therefore the area under the glucose response curve for 50 g glucose solution (AUCg) was equal to: (51.5 + 37.6/2) × 30 + (37.6+ 24.5) × 30/2 + (24.5 + 11) × 30/2 = 4762.75 mg/minute/dL The AUC for Neo-Mune (AUCn) was equal to: (32.6 + 11.9/2) × 30 + (11.9+16.6 + 6.0/2) × 30 = 2101.5 mg/ /dL The AUC ratio is equal to: AUCn/AUCg x 100 = (2101.5/4762.75) × 100 = 42.12. This means that consuming Neo-Mune raises plasma glucose 57.88% less than consuming the glucose solution. Therefore, the GI of Neo-Mune is 42.12 falling in the category of a low-GI food according to advisory guidelines. No adverse events occurred during the study.

Discussion

Assuming that Neo-Mune would have a low-GI was reasonable because of its composition. It contains fructose, instead of sucrose or polydextrose. Fructose helps to facilitate glucose clearance from plasma by forming fructose-1-phosphate by the liver. Fructose-1-phosphate activates glucokinase in the liver which catalyzes the phosphorylation of glucose into glucose-6-phosphate and subsequently enables it to be stored as glycogen in the liver, thus blunting the postprandial increment in plasma glucose levels.[5]

The presence of polydextrose may also play a role in

decreasing glucose response.[6] Polydextrose is a functional fiber which is not hydrolyzed by human digestive enzymes in the small intestine but partially fermented by endogenous microbiota in the colon to produce short chain fatty acids. Therefore, it has an energy contribution of only 1 kcal/g.[7]

Although polydextrose is not sweet, it can replace sugar, fat and calories. Not only has it been used as a low calorie bulking agent in a variety of foods including baked foods, dairy products and functional beverages, but also as a fiber content increment in processed food. Due to its laxative and satiety effects,[8] polydextrose functions as both a stabilizer and bulking agent, and helps to maintain moisture in food.[9] The glycemic index of polydextrose is only 7[10] and clinical trials have demonstrated that polydextrose has beneficial effects on appetite, satiety and energy intake.[11,12]

Regular consumption of high GI meals compared with isoenergetic and nutrient-controlled low GI meals, results in higher average 24-hour plasma glucose and insulin levels, higher C-peptide excursion and higher HbA1c in both diabetic and nondiabetic subjects.[13] Hyperinsulinemia may cause insulin resistance and consequently β-cell failure.[14] Salmeron J, et al.[15] conducted a cohort study surveying 65,173 women in the US aged 40-65 years old who had no cardiovascular disease, cancer or DM, and 42,759 men aged 40-75 years old who had no DM or cardiovascular disease.[16]

Subjects were asked to complete a dietary questionnaire over a 6-year period. The results revealed that dietary GI was positively associated with the risk of developing DM after adjusting for other confounding factors. The relative risk (RR) of developing DM in women was 1.37 (p=0.005) and in men was 1.37 (p = 0.03).

Jarvi AE, et al.[17] conducted a randomized crossover study of 20 subjects with type 2 DM by providing different GI diets during 2 consecutive 24-day periods. Both diets had the same macronutrient composition and the same type and quantity of dietary fiber. The results showed that peripheral insulin sensitivity increased significantly and fasting plasma glucose decreased during both periods.The incremental area under the curve for both glucose and insulin was 30% lower in low GI diets compared with high GI diets. LDL-C was significantly lower in both diets; however, low-GI diets were significantly lower. Brand JC, et al.[18] conducted a crossover study to evaluate the effects of low GI and high GI diets on long term glycemic control over two 12-week periods among patients with type 2 DM and found that glycemic control was improved among those on the low GI diets compared with the high GI diets ($p < 0.05$). Mean HbA1c at the end of the low GI diets was 11% lower (7.0 ± 0.3%) than at the end of the high GI diets (7.9 ± 0.5%). However, mean fasting plasma glucose, total cholesterol, triglycerides, HDL-C and LDL-C did not significantly differ between groups. Willett W, et al.[19] reviewed metabolic and epidemiologic studies and found that replacing high GI with low GI carbohydrate diets reduced the risk of type 2 DM. Among patients with DM, replacing high GI with low GI carbohydrates improved glycemic control and reduced hypoglycemic episodes among those treated with insulin. Luscombe ND, et al.[20] examined the effects of high and low GI carbohydrate diets, and monounsaturated fats (MUFA) in 14 subjects with type 2 DM in a random crossover design study for 4 weeks. They demonstrated that HDL-C levels were significantly higher in the subjects on the low GI and high MUFA diets compared with the high GI diet. No significant difference was observed in metabolic control between the diets, even after adjusting BMI, glucose control and sex. Bouch´e C, et al.[21] evaluated whether 5 weeks on a low GI diet versus a high GI diet could affect glucose and lipid metabolism as well as total fat mass among 11 nondiabetic men using a crossover design with a 5-week washout period. They confirmed that the low GI diet resulted in lower postprandial plasma glucose levels, insulin profiles and areas under the glucose curve (AUC) than the high GI diet (p <0.05). The low GI diet was associated with a decrease in the total fat mass (p <0.05) and a tendency to increase lean body mass (p <0.07) without any change in body weight and a reduction in leptin, lipoprotein lipase and hormone-sensitive lipase mRNA in subcutaneous abdominal adipose tissue. Therefore, low GI diets might play a role in preventing metabolic diseases and cardiovascular complications. Yanai H, et al.[22] assessed the effects of carbohydrate and dietary fiber intake, glycemic index (GI) and glycemic load (GL)on HDL-C metabolism by reviewing meta-analyses and clinical studies in an Asian population. They concluded that low carbohydrate intake, GI and GL, as well as high dietary fiber might be beneficially associated with HDL-C metabolism in Asian populations.

Barclay WA, et al.[23] evaluated the association between GI, GL and chronic disease risk by performing a meta-analysis including 37 prospective cohort studies resulting in a total of 40,129 subjects. They illustrated that low GI and/or low GL diets were independently associated with reduced risk of certain chronic diseases including DM, coronary heart disease, gall bladder disease and breast cancer.

Therefore, maintaining low GI diets in the long term should confer greater benefits than high GI diets in many ways, including decreasing the glucose-insulin response, increasing insulin sensitivity, improving lipid profiles (higher HDL-C and lower LDL-C), decreasing fat mass and reducing the risk of developing diabetes, certain cancers and cardiovascular disease.

The present study enrolled a small sample size with limitations regarding statistical validity. It would be useful to repeat the exercise with a larger sample, possibly over a larger age group to obtain more detailed transferrable information, in particular, for patients with diabetes. It comprised a cross-sectional study, not a long term study. Further study of Neo-Mune concerning long term metabolic outcomes is warranted.

Conclusion

The present study showed that Neo-Mune has a low GI food. Neo-Mune has been recommended to cancer or critically ill patients to enhance their immune function. These groups of patients might also have underlying conditions including DM or stress-induced or medication-induced hyperglycemia. Therefore, confirming that Neo-Mune consumption would not have a negative impact on their glycemic control was necessary and indeed might actually help patients with diabetes control their plasma glucose more easily than those consuming standard oral or enteral nutrition. However, further study of Neo-Mune on long term metabolic outcomes is warranted.

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Declaration of conflicting interests

The author declares that no potential conflicts of interest exist with respect to the research, authorship and/or publication of this article.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Supplementary Materials

Data on the subjects has been kept safely with the principle investigator. The case record forms included only patients' initials and surname and number, not their full name.

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ASSOCIATION BETWEEN CORE MUSCLES AND THE 400-METER OVERGROUND SPRINTING VELOCITY AMONG WHEELCHAIR RACERS

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Abstract

Objective: The study aimed to measure the activity of the core muscles and middle trapezius in T54 class wheelchair racers during full effort over ground sprinting and to determine its association with propulsion velocity.

Methods: Eight male international wheelchair racers, having normal upper limb and partial to normal trunk function (T54 class athletes), propelled their racing wheelchairs on a 400-m competition track with maximal effort. Electromyography (EMG) of the rectus abdominis (RA), iliocostalis lumborum (IL), longissimus thoracis (LT) and middle trapezius (MT) were recorded at each 100 m reach using a wireless surface EMG recorder. Percentage of maximal voluntary contraction (%MVC) was measured and correlated with propulsion velocity.

Results: Median %MVC of RA, IL, LT and MT were 54.2, 43.9, 30.6 and 35.6%, respectively. A positive association to propulsion velocity was found in RA ($p = 0.04$, $r = 0.73$) while a negative association to propulsion velocity was also found in MT ($p = 0.03$, $r = -0.77$).

Conclusion: Abdominal function was activated most and associated with propulsion velocity among male T54 class wheelchair racers. In addition, optimizing scapular retraction may benefit propulsion velocity.

Keywords : Athlete athletics, Disabilities, Paraplegia, Sports, Propulsion

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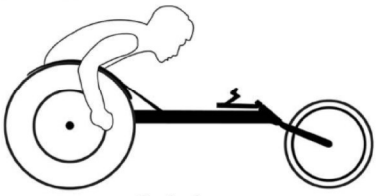
Introduction

Wheelchair racing is an international sports competition for people with physical challenges. In spite of its popularity among athletes and spectators, the complexity of wheelchair racing propulsion is still not totally understood; and thus, no ideal racing stroke pattern has been commonly accepted. [1] Unlike able-bodied athletes, wheelchair racers comprise athletes with spinal cord injury, poliomyelitis, cerebral palsy and limb dysfunction. This wide range of physical impairments in terms of muscle weakness, spasticity, joint contracture and spinal deformity leads to vast variations of propulsion styles among athletes. Therefore, for coaches and sport professionals to design an effective training program for wheelchair racers remains challenging.

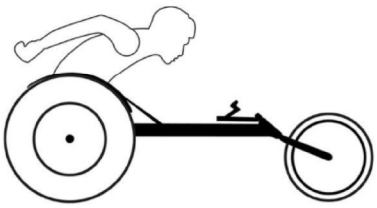
Most articles regarding the wheelchair racing sport regard propulsion technique as the key to racing performance. [2] This idea might be supported by results from related investigations. Researchers found in a longitudinal study that after six months of training, a group of wheelchair racers propelled faster without any significant change in muscular power and anaerobic capacity.[3] Related investigations revealed that, to propel faster, wheelchair racers needed fast and precise hand contact and to lean the trunk forward.[2, 4-7] In spite of extensive studies, the perfect wheelchair racing stroke has not been completely achieved yet. Most articles have focused on kinesiology and upper extremities work rather than the function of the trunk and scapular musculature which, physiologically, should be another substantial part of propulsion mechanisms. The significance of the core muscles is an issue of interest in sports science.[10-12] Apart from its function as a dynamic stabilizer protecting the spine from injury, some literature regards the core musculature as the power house of the body.[13-15] Although less research has demonstrated the benefits of core training for elite athletes; [16] its relationship to exercise performance has been reported among some athletes such as runners and handball and soccer players. [17-19] It has been shown that healthy subjects propelled regular wheelchairs with energy transferred from the trunk.[20] For wheelchair racing propulsion, increased trunk flexion angle at the initial contact was observed as speed increased.[7] However, core muscles activation during the racing propulsion has never been investigated. Therefore, the significance of the core muscles in racing seems to be a general opinion rather than an established scientific conclusion. Physiologically, the effective energy from the core muscles possibly maximizes the body's kinetic chains; thereby, promoting effective movements of the upper and lower limbs.[14, 15] In fact, rhythmic trunk movement can always be visualized both in racing competition and the laboratory.[1] Hence, the core muscles are certainly activated. The question remains whether the core muscles function contributes to propulsion velocity or is just to maintain the trunk at optimal posture.

The scapular stabilizers are regarded as substantial musculature for upper extremity sports. They provide a stable base for efficient glenohumeral motion through which energy from the trunk can be transferred to the upper extremities.[21-23] However, this musculature seems to have received less attention from most researchers concerning wheelchair biomechanics. One propulsion cycle comprises push and recovery phases determined by hand contact and release from the wheel, respectively (**Figure1**). It was shown that the middle trapezius (MT); one of the scapular stabilizers; begins its contraction in the push phase then continues working through the recovery phase of regular wheelchair propulsion.[24] Thus, the MT probably functions as a link between the trunk and the upper extremity particularly during vigorous activity such as high speed racing wheelchair propulsion. The question is whether or not the MT contributes to racing wheelchair propulsion velocity. More understanding of the core muscles and MT function would provide additional scientific clues for sports professionals to design a training program that genuinely maximizes the athletes' performance. The authors hypothesize that the magnitude of the function of the abdominal, paraspinal and MT muscles would be associated with racing wheelchair propulsion velocity. The aim of the study was to measure activities of the core muscles and MT in T54 class wheelchair racers during racing wheelchair propulsion and to determine its association with propulsion velocity.

Figure 1. Graphics showing racing wheelchair propulsion pattern push and recovery phases are determined by hand contact and release from the wheel, respectively. Among T54 class wheelchair racers, the trunk always moves in the sagittal plane. Magnitude of trunk movement varies among individuals.



Push phase



Recovery phase

Methods

This observational study was conducted to determine the association between racing wheelchair propulsion velocity and the relative magnitude of the core muscles and MT activities. Trunk flexor and extensors were selected because the trunk moves mainly in the sagittal plane during racing wheelchair propulsion.[1, 6] The MT as the scapular stabilizer activated in both push and recovery phases, might be part of the mechanism associated with propulsion velocity. To create an environment similar to wheelchair racing competition, we conducted the study on a standard racing track using the same start and finish line as used in real competition. Recording relative muscle activity and propulsion velocity every 100 m reach allowed performance, while accelerating and maintaining at high speed, to be observed. In response to the hypotheses, the authors correlated propulsion velocity with the relative magnitude of muscle activity at each 100 m reach to find possible associations between propulsion speed and relative muscle function.

Subjects

The ethics of the present study was approved by the Institutional Review Board, Royal Thai Army Medical Department and all ethics guidelines were followed by the authors. Subjects were informed of the benefits and risks of the investigation before signing an institutionally approved informed consent document to participate in the study. Subjects comprised eight male international wheelchair racers of class T54 on the Thai national team. According to the International Paralympic Committee (IPC) athletics classification rules, T54 wheelchair racers refer to athletes who have normal upper limb function with a range of trunk function extending from partial to normal.[25] Classification was confirmed earlier by IPC classifiers. Subjects were excluded from the study if they were injured to the extent that would interfere with their performance. All subjects received a diagnosis of poliomyelitis. Average age was 29±4.81 years and all subjects received the same training and nutrition program. A minimum of eight hours sleep including adequate hydration was ensured before measurement. Subjects' characteristics are shown in **Table 1**.

Table 1. Demographic data and overall propulsion performance of each subject

subject	age	Body weight (kg)	abdominal muscle	paraspinal muscle	propulsion velocity in 400 m (m/sec)
# 1	25	58.9	normal	normal	8.23
# 2	23	41.4	normal	normal	8.05
# 3	28	39.4	normal	partial*	8.00
# 4	36	58.7	normal	normal	7.96
# 5	32	51.7	partial*	partial*	7.74
# 6	24	42.4	normal	normal	7.68
# 7	30	44.6	normal	normal	7.46
# 8	34	54.0	normal	normal	7.24

*Partial = presence of partially atrophic muscle

Training Program

The training program comprised overground propulsion training and weight training. Overground propulsion training was practiced six days weekly in the morning and evening. The program started with 30 to 60 minutes of slow speed propulsion as a warm-up followed by 30 to 60 minutes of alternate high and low speed propulsion. Short distance sprinting and starting propulsion training were added occasionally. Daily training ended with 30 minutes of very slow speed propulsion to cool down. Approximately 20 km distance endurance propulsion was supplemented once weekly. The weight training program comprised two sessions each week of approximately 60 minutes training using resistance between 10 to 15 repetitions maximum. The program aimed to strengthen the shoulder girdle and upper extremity musculature. In addition, supine abdominal curls and prone trunk extension exercise were practiced approximately 20 minutes to maintain trunk muscle strength.

Instrumentation

To measure relative muscle activity, the authors used a portable surface electromyography (MegaWin® ME3000P, Kuopeo, Finland). The skin at the recording site was shaved and cleaned with an alcohol wipe before measurement. Pairs of pre-gelled silver-silver chloride surface electrodes (Red Dot 2258-3, 3M, Ontario, CA, USA) were placed on the muscles of interest unilaterally with a center-to-center distance of 2 cm. Electromyography (EMG) data was sampled at a rate of 1 kHz with 12-bit analog to digital conversion and bandpass filtered at 8 to 500 Hz. EMG signals were recorded in a memory card within a portable machine (compact flash memory, 4Mb) before transferring to a computer to analyze using MegaWin Software, Version 3.2. The magnitude of muscle activity during propulsion was compared with maximal isometric voluntary contraction (MVC) and presented as a percentage of maximal voluntary contraction (% MVC).

Procedures

The study was conducted on a standard 400 m competition track during the afternoon on three consecutive days. Subjects spent approximately 15 minutes of warm-up comprising upper extremity stretching and slow propulsion on the track. Initially, measurement of MVC was performed on a bench. Subjects were asked to perform three trials of maximal isometric contractions against manual resistance. EMG signals from the middle 2 seconds of a 6-second contraction were recorded and then averaged over three trials. For the longissimus thoracis (LT) muscle, the electrodes were placed at a two-finger width lateral from the spinous process of L1. Subjects lifted the trunk from a prone position against manual resistance. For the iliocostalis lumborum (IL) muscle, the electrodes were placed at one-finger width medial from the line between the posterior superior iliac spine and the lowest point of the lower rib at the level of L2. The subject lifted the trunk from a prone position against manual resistance. For the rectus abdominis (RA) muscle, electrodes were placed 3 cm apart and parallel to the muscle fibers so that they were located approximately 2 cm lateral and across from the umbilicus over the muscle belly. From the supine posture with hips and knees stabilized in the flex position, subjects performed a curl-up against manual resistance. For the MT muscle, the electrodes were placed at the midpoint between the medial border of the scapula and the spine at the level of T3. In the prone position, subjects abducted their shoulders horizontally before performing scapular retraction against manual resistance.[26-27] Immediately after MVC measurements, subjects spent approximately 5 minutes propelling on the racing track to be familiar with the wires and electrodes attached to the trunk. To measure muscle activity during propulsion on the racing track, subjects were asked to perform full-effort overground propulsion on the standard 400 m racing track using their own wheelchairs. EMG signals from each muscle were recorded using a portable recorder securely attached to the rear frame of the racing wheelchair. The 400 m propulsion time was measured using a manual stopwatch. One lap distance was equally divided in four 100 m reaches represented by D-1 to D-4. All subjects propelled in lane 3 starting by the curved track and finished by the straight track (**Figure 2**).

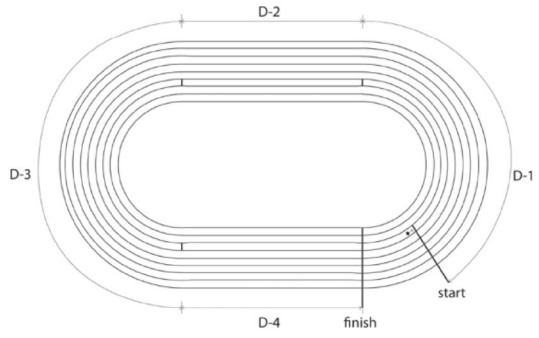


Fig 2. Graphics demonstrating experimental set-up

D-1 = distance from 0 to100 m, D-2 = distance from 100 to 200 m

D-3 = distance from 200 to 300 m, D-4 = distance from 300 to 400 m

Propulsion time in each 100 m reach was recorded using a satellite-connecting stopwatch (Garmin Forerunner® 305, Olathe, KS, USA) attached to the racing wheelchairs. The satellite-connecting stopwatch recorded the time spent within each 100 m distance. After finishing, EMG data were transferred to computer to analyze. EMG data from each 100 m reach was averaged and presented as % MVC. Propulsion velocity in each 100 m reach was correlated with the % MVC of that reach.

Statistical Analysis

For descriptive statistics, data were presented in number and percentage. Continuous data with normal distribution was presented as mean and standard deviation. The % MVC was presented as a median value (min-max). For analytical statistics, the Friedman test was used to compare the % MVC of each muscle in each 100 m distance. Association between the % MVC of each muscle and the velocity was analyzed by Spearman's rank correlation. The alpha level of significance was set at a p value of <0.05. All statistical analyses were performed using STATA/MP, Version12.

Results

Subjects performed 400 m racing wheelchair propulsion with mean propulsion time of 51.47±2.25 s. Mean propulsion time was longest in the D-1 (17.75±1.49 s) then became relatively constant during the D-2 to D-4 (11.38±0.52, 11.50±2.62 and 11.25±1.04 s, respectively). Notably, each subject had individual patterns of relative muscle activation (**Figure 3**).Throughout 400 m propulsion, median %MVC in the RA muscle was the highest, followed by the IL, MT then LT. However, no significant difference of %MVC was found among these four muscles (**Figure 4**).

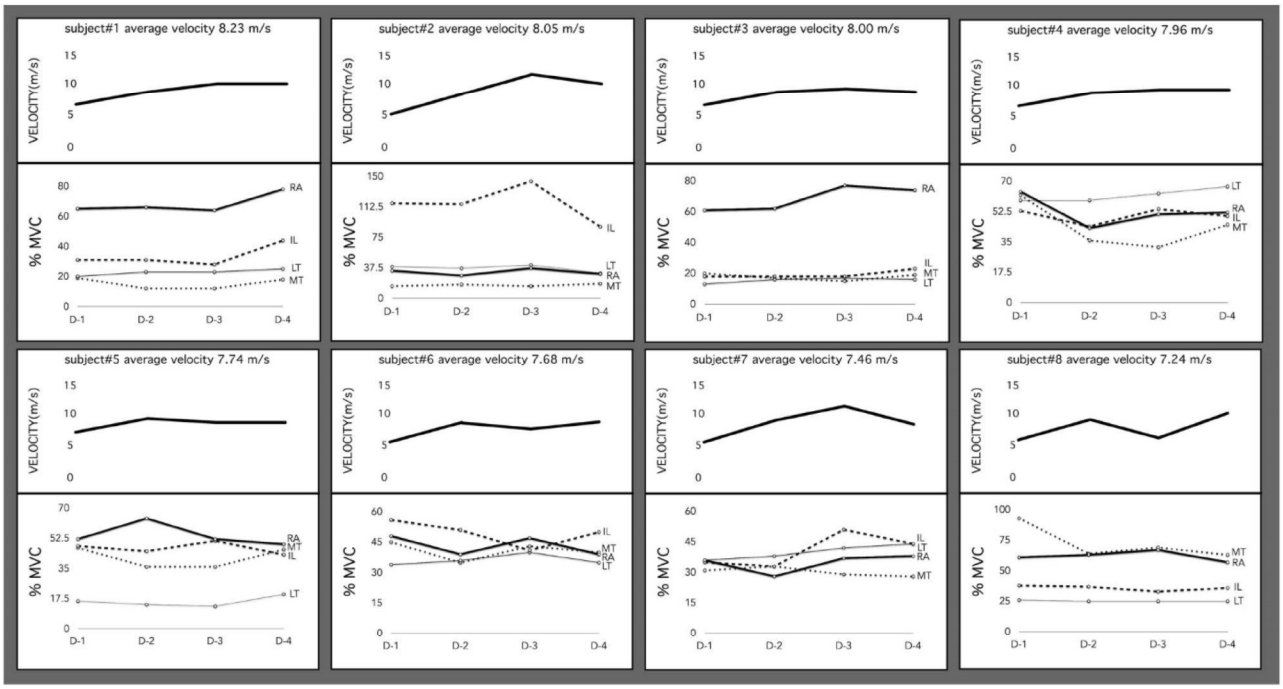


Fig 3. Muscle activation and propulsion speed of each subject

RA = rectus abdominis, IL = iliocostalis lumborum, LT = longissimus thoracis, MT = middle trapezius

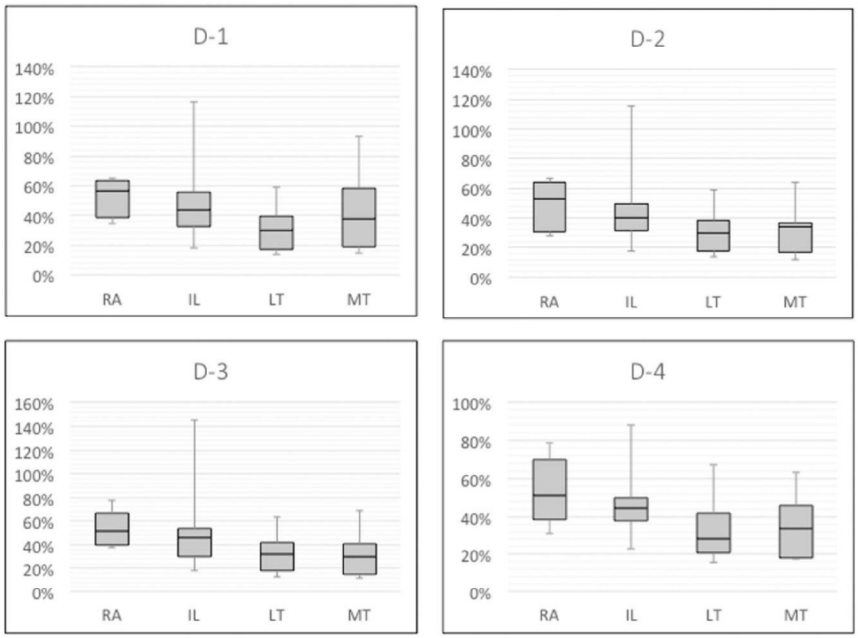


Fig 4. Median % MVC of each muscle
RA = rectus abdominis, IL = iliocostalis lumborum, LT = longissimus thoracis, MT = middle trapezius

When propulsion velocities were correlated with % MVC in each reach, the authors found a significant positive association between % MVC of the RA muscle and propulsion velocity in the D-1 reach ($p = 0.04$, $r = 0.73$). No significant association was found between %MVC of the RA and propulsion velocity in the D-2, D-3 and D-4 reach. Also, a negative association was observed between %MVC of the MT muscle and propulsion velocity in the D-3 reach ($p = 0.03$, $r = -0.77$). Moreover, no significant association was observed between %MVC of the MT and propulsion velocity in the D-1, D-2 and D-4 reach, and no significant association between propulsion velocity and % MVC was found in the IL and LT muscles throughout the 400 m propulsion.

Discussion

Faster athletes had a tendency to use more abdominal muscle than slower ones. The results not only provided initial scientific evidence indicating the significance of the abdominal muscle to racing wheelchair propulsion but also explained the previous observation that trunk flexion at the initial hand contact increased as speed increased.[7] It might be the energy transferred from the contracting abdominal muscle that promotes powerful upper extremity push.[20] Interestingly, a significant association occurred only in the first 100 m but not in the remaining 300 m. This might indicate that abdominal function is substantial for starting acceleration propulsion but contributing less to performance in the relatively constant speed phase. Other factors might contribute to success in this phase. Level of association by 0.73 between abdominal function and propulsion velocity indicated that only one half of the subjects propelled under this association in the present study. Based on these results, abdominal function of T54 wheelchair racers may need to be promoted particularly for athletes intending to improve starting acceleration performance.

The relative magnitude of the back muscles such as the IL and LT activities were not associated with racing wheelchair propulsion velocity in the present study. Therefore, strong exertion of the back muscles may not benefit wheelchair racing speed. The result was irrelevant to part of our hypotheses. A study of starting propulsion analysis in a wheelchair racer revealed that the trunk extended away from the pushing hands after reaching its peak flexion, occurring approximately at the point of hand contact.[1] To the authors' best knowledge, the role of the back muscles in racing propulsion has never been investigated. However, based on our results, the authors propose that the main function

of the back muscles is to provide a relatively stable base for the push rather than giving out energy to the extremities. The lack of association with propulsion speed for the back muscles seems to be related to motion in racing propulsion, performed mainly by pushing rather than pulling (**Figure1**). Although the relative magnitude of the back muscle function was not associated with 400 m wheelchair racing speed, the back muscles were contracting throughout the 400 m distance. Therefore, this may provide a clue that the back muscles may need more endurance than strength or coordination training. Notably, during the first 100 m of acceleration, propulsion velocity was associated only with the abdominal not with the back muscles function. This might indicate that abdominal function is more important than back muscle function in T54 class wheelchair racers competing in the 400 m race.

The authors hypothesized that faster wheelchair racers would exert the MT at a greater magnitude. Unexpectedly, the results showed that the slower subjects had a tendency to use more MT, contrary to the hypothesis. This may indicate that strong exertion of the MT is not only unnecessary but also related to the mechanisms that hinder propulsion speed. Notably, a significant association occurred only in the third 100 m curve track. The authors assumed that some differences may exist in mechanisms between high speed propulsion on the straight and curve tracks. As a result, the authors propose that the main function of the MT in wheelchair sprinting is to navigate scapular motion rather than give out energy to propel. Slower subjects not only tended to use more MT but also showed less speed consistency after 200 m (**Figure 3**). This speed variability may be due to fatigue. Based on our results, overly strong scapular retraction does not seem to produce a decent stroke pattern among T54 class wheelchair racers. Future research should focus more on the role of scapular motion during racing wheelchair propulsion.

Full effort overground racing propulsion on a standard racing track has created more realistic conditions than those in the laboratory setting.[2, 4] In addition, only four sets of electrodes attached to the trunk should have allowed subjects to propel naturally so that the muscle activation and coordination were greatly similar to that of real competition. However, a study conducted outside the laboratory might be influenced by uncontrolled environmental factors especially wind. Propulsion times recorded from each subject that were close to his personal best reflected that subjects propelled wheelchairs with nearly maximal exertion. Based on IPC classification, T54 athletes can be individuals with poliomyelitis, spinal cord injury and lower limb amputation or dysfunction. These physical differences may influence propulsion style or performance. While athletes with poliomyelitis generally have lower body weight due to massive muscle wasting, heavier amputated wheelchair racers may propel with isometric contraction of the remaining lower limb muscles and spinal cord injured athletes may be challenged by muscle spasticity. Unfortunately, only subjects with poliomyelitis were enrolled in the present study. In fact, classifications for wheelchair racers are determined by disabilities not by diseases. Currently, the IPC considers all lower limb variations as comparable disabilities for T54 wheelchair racers.[29] According to the definition of T54 class wheelchair racers, intra-class variations of the trunk function extend from partial to normal. Whether intraclass variations significantly influence muscle activation remains unknown. The characteristics of our subjects were fairly homogeneous in terms of their physical disabilities as well as training protocols provided. However, variations of the trunk muscle exertion were still observed. We believe that this was not due to physical differences among subjects. This might be attributed to the lack of knowledge of how to properly exert trunk muscles. Based on the characteristics of subjects in the present study, our results were established from athletes with full to nearly full trunk function. Therefore, findings from the present study may not represent individuals with poor trunk function. The study design provided only initial scientific evidence showing the significance of the relative core muscles and MT function in wheelchair racing velocity. Therefore, the present study is not considered as strong evidence demonstrating the effects of core activation styles because an association cannot determine the cause or effect of an event. Further prospective randomized placebo-controlled trials are still required to demonstrate the effects of core activation style or training protocols concerning wheelchair racing performance. However, the authors believe that the results from the present study have provided initial knowledge for practitioners and investigators in this area.

The small sample size may have reduced the power of statistical significance and caused the results to be less generalized. Findings from the present study should be applied with caution to athletes of other conditions such as female athletes, individuals with poor trunk function or impaired upper limb function. Results from the present study provided initial evidence that the magnitude of abdominal function was associated with propulsion velocity at the first 100 m among male T54 class wheelchair racers with poliomyelitis. Therefore, abdominal function while propelling should be promoted whereas optimizing scapular retraction may benefit propulsion velocity. The authors recommend that, apart from overground practice, a wheelchair roller or treadmill with biofeedback could be used to cultivate the proper trunk and MT muscle function.

Conclusion

Abdominal function was activated most and associated with propulsion velocity among male T54 class wheelchair racers. In addition, optimizing scapular retraction may benefit propulsion velocity.

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FACTORS RELATED TO BLOOD LOSS IN TOTAL KNEE ARTHROPLASTY

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Abstract

Background: Mainly the elderly undergo total knee arthroplasty (TKA) which entails risks from medical procedures and conditions. The reported amount of blood loss in TKA varies in different studies. Blood loss from TKA may change hemodynamic status, leading to risk of cardiovascular morbidity or mortality. Allogeneic blood transfusion, associated with many immunological and transfusion complications, increase surgery costs. Controlling factors associated with blood loss should decrease blood loss and complications.

Objectives: Determining risk factors for blood loss constitute a significant step toward blood management. This study also used calculated blood loss, which is more accurate than visible blood loss.

Methods: Medical records of 517 patients undergoing TKA from 2011 to 2016 were examined, and blood loss was calculated using Gross' formula. Pearson's correlation and multiple regression analyses were used to identify factors associated with blood loss.

Results: The mean calculated blood loss decreased yearly from 602.94ml to 107.78ml in 2016 with "zero" transfusions in 2016. Radivac drain, patellar resurfacing, modified Robert Jones bandage and higher postoperative pain score related to increased blood loss after TKA according to Pearson's correlation. Multiple regression analysis revealed significant independent predictors related to blood loss included radivac drain, intravenous tranexamic acid, postoperative pain score and body mass index (BMI).

Conclusion: Awareness of low BMI patients, avoiding radivac drain use, routine using of intravenous tranexamic acid and good postoperative pain control could reduce blood loss and transfusions for patients undergoing TKA.

Keywords : Blood loss, TKA, Radivac drain, Transfusion, Tranexamic acid

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Introduction

Total knee arthroplasty (TKA) is a major orthopedic operation for advanced stage osteoarthritis of the knee. Increasing occurrence of this operation by average age of the patients has been observed, including the comorbidity and aging process, followed by increasing number of its complications. One serious complication is perioperative blood loss. Total knee arthroplasty (TKA) is an operation involving significant blood loss because of extensive soft tissue release and bone cuts, varying from 500 to 1900 ml. In all, 9.8% of cases needed postoperative blood transfusion.[1] Blood loss from TKA may change the hemodynamic status of patients at risk of cardiovascular morbidity or mortality. Allogeneic blood transfusion is also associated with many immunological and transfusion complications such as risk of HIV transmission and mismatch complications.[7] Even autologous transfusion is presents risk, autologous donors as a group tend to be older and less healthy, thereby increasing the chance of complications during donation, and risk of unrecognized bacteremia at the time of blood collection.[13] Autologous transfusion may actually lead to decreased hemoglobin levels postoperatively, resulting in transfusion of autologous blood among patients who, if they had not donated and thus lowered their hemoglobin level before surgery, would not have needed the transfusion. Autologous transfusion also causes the unnecessary waste of blood and expenses. Significant blood loss from TKA is not from perioperative or suction drain but from invisible blood loss or concealed hemorrhage. Invisible blood loss is from hemolysis, blood permeating into interstitial fluid and concealed blood in intraarticular space, can total more than 500 mL.[2, 3] Visible blood loss seen during the intraoperative period and during the postoperative period, the suction drain accounts for approximately one half of the total amount of blood loss of each patient calculated by formula.[4] Gross's formula for calculating the total blood loss is the most popular at present [4, 6], so we choose to use this formula. The time to collect blood to calculate was from the 4th to 7th postoperative day whichever was the lowest. To reduce the risks from blood transfusion and reduce costs, would constitute the best way to reduce blood loss. We retrospectively studied our patients' data and determined factors associated with blood loss in TKA to prepare and find the best solution to reduce blood loss among our patients.

Methods

The authors retrospectively analyzed 517 consecutive patients undergoing TKA between January 2011 and December 2016 at Phyathai 2 International Hospital. The sample size was calculated using the program G*Power 3.1.[24] The sample size totaled 189 patients (**Figures 1, 2**). The research team used purposive sampling to select the 517 patients. All patients were admitted for an elective TKA by a single experienced surgeon using a primary diagnosis of advanced osteoarthritis or rheumatoid arthritis refractory to include conservative management in the study. Patients undergoing revision arthroplasty or having another orthopedic procedure in addition to TKA during one anesthetic session, as well as patients with missing relevant clinical information were excluded from the study.

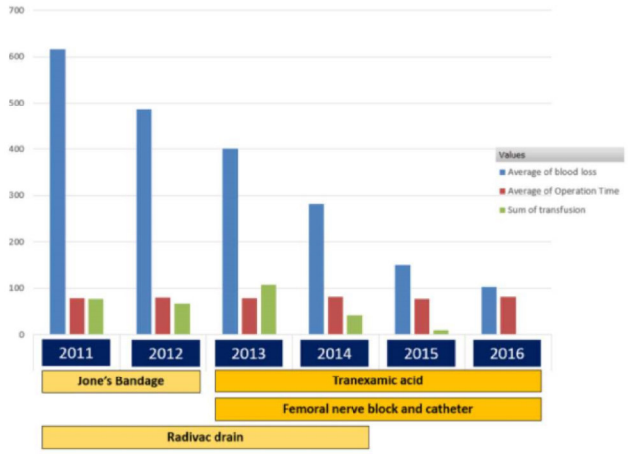

Fig 1. Trend of average blood loss reduced yearly with timeline of protocol

Data were obtained from the medical records of all patients included in the study. Data variables studied included patient demographics, body mass index (BMI), concomitant comorbidities (categorized as with or without comorbidity), length of stay, blood transfusion, preoperative hemoglobin (Hb), postoperative hemoglobin (4th day postoperative), operative times, use of drain, using of tranexamic acid, patellar resurfacing, applied modified Robert Jones bandage, postoperative pain level in the first 48 hours and femoral nerve block. The standard technique was used in all cases. The procedure was performed under spinal/epidural

anesthesia and a tourniquet was inflated 100 mmHg above the systolic blood pressure among all patients. An anterior midline skin incision and a medial parapatellar arthrotomy were performed. To reduce the intraoperative blood loss from the femoral hole, an intramedullary plug with bone grafts was used.[12] The implant used was a posterior, stabilized, cemented knee prosthesis. Periarticular bupivacaine injection was performed without adding adrenaline. The tourniquet was used in all cases inflated to 350 mmHg then partially deflated to 250 mmHg after fascia closure to reduce risk of postoperative thigh pain. All patients received tranexamic acid (starting from 2013) 10 mg/kg body weight, one dose after starting anesthesia and one dose before skin closure. The antibiotic prophylaxis consisted of 2 g of cefazoline administrated within 1 hour before starting the surgery and 1 g every 6 hours during the 24 hours postoperative. Among patients allergic to penicillin, we employed 1 g of vancomycin 1 hour before surgery followed by 1 g every 12 hours over 24 hours. When a radivac suction drain was inserted inside the joint it would be removed after 24 hours. Postoperative pain control was achieved by cold compression with Cryocuff, intravenous and oral NSAIDs and pregabalin the first and second postoperative days. Intravenous opioid was used when pain did not improve. The team comprising a cardiologist, orthopedist and an anesthesiologist assessed all patients postoperatively. Range of motion exercise was started on first postoperative day and full weight-bearing mobilization was started on the second day assisted by a physiotherapist. Any patient presenting a postoperative hemoglobin value of less than 8.0 g/dl received a blood transfusion.

Venous thromboembolism (VTE) prophylaxis protocol was started immediately in all cases by intermittent pneumatic compressive device and ankle pumping. Chemoprophylaxis for VTE was started the second postoperative day using oral anticoagulant (Apixaban, Rivaroxaban) for 14 days.

Gross' formula was used to calculate total blood loss with hematocrit the fourth postoperative day

Total blood loss = Blood volume x [(Hct preop - Hct postop) / Hct average] + ml transfused RBC

Blood volume

Male: 604 + 0.0003668 x size3 (cm3) + 32. 2 x weight (kg)

Female: 183 + 0.000356 x size3 (cm3) + 33 x weight (kg)

Statistical analysis

All data analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA) to carry out Pearson's correlation. The size of the combined correlation coefficient (r value) reflected the degree of the relationship between an index and the other indexes, indicating the relative reliability of the method.[23] All values were calculated as mean ± standard deviation. A *P* value less than 0.05 was considered significant. Multiple regression analysis was used for all statistical calculations. Estimated blood loss was measured employed Gross' formula, which used the maximum postoperative decrease in the level of hemoglobin adjusted by the weight and height of the patient.[8]

Results

Data from 517 patients were collected from January 2011 to December 2016. Patient characteristics revealed 85% were female and 15% male. Mean age was 70±8 years old, mean BMI was 27±4 and mean operative time was 86±25 minutes. Preoperative Hb was 12.58±1.35 g/dl while postoperative Hb was 11.32±1.19 g/dl. Average calculated total blood loss was 323±243 ml. The average blood loss in each data group is summarized in **Table 1**. The trend of average blood loss decreased yearly from 2011 to 2016 as shown in graph1, i.e., 602.94 mL in 2011, 476.41 mL in 2012, 406.64 mL in 2013, 286.28 mL in 2014, 149.4 mL in 2015 and 107.78 mL in 2016. The average operative times were close, ranging from 76 to 84 minutes. The number of blood transfusion decreased to "zero" in 2016. The modified Robert Jones bandage was used from 2011 to 2012 then use stopped. The radivac drain was used from 2011 to 2013 then stopped. In addition, intravenous tranexamic acid, femoral nerve block and catheter were used from 2012. Pearson's correlation showed five factors influenced blood loss in TKA, namely, radivac drain (r=0.452**, p=0.01), tranexamic acid (r = -0.410**, p = 0.01), patellar resurface (r = 0.115**, p = 0.01), modified Robert Jones bandage r=0.185**, p=0.01) and postoperative pain score (r = 0.136**, p = 0.01). Radivac drain, patellar resurface, modified Robert Jones bandage, radivac drain, patellar resurface and postoperative pain score showed a similar trend involving blood loss, namely, more blood loss occurred when number or uses increased. Intravenous tranexamic acid use was related to less blood loss.

Table 1. Average blood loss in each group of patients

Factors	a	b	SE.b	BETA	t	R^2	F
Constant	392.622					0.328	62.593**
X_1 Radivac drain		196.764	18.845	.387	10.441**		
X_2 Tranexamic acid		-163.158	18.359	-.329	-8.887**		
X_3 Postoperative pain score		14.221	4.834	.108	2.942**		
X_4 BMI		-4.366	1.973	-.081	-2.213*		

After employing multiple regression analysis to determine the correlation and predictive equation of blood loss, only four factors were found to influence blood loss, i.e., radivac drain (t=10.441, p=0.01), tranexamic acid (t = -8.887, p = 0.01), postoperative pain score (t =2.942, p = 0.01) and BMI (t = -2.213, p = 0.05).

$$\text{Blood loss after TKA} = 392.622 + 196.764\,X_1 - 163.158\,X_2 + 14.221\,X_3 - 4.366\,X_4$$

Discussion

TKA is an operation involving significant blood loss, varying from 500 to 1900 ml. Approximately 9.8% of patients needed postoperative blood transfusion.[1] Blood loss from TKA may change the hemodynamic status of patients at risk of cardiovascular morbidity or mortality. Allogeneic blood transfusion is also associated with many immunologic and transfusion complications such as risk of HIV transmission and mismatch complications.[11] Autologous transfusion increases the chance of complications during donation, and risk of unrecognized bacteremia at the time of blood collection.[13] Autologous transfusion may actually lead to decreased hemoglobin levels postoperatively, resulting in a transfusion of autologous blood among people who would not have needed a transfusion. Autologous transfusion also causes the unnecessary waste of blood and expenses.

Blood loss from TKA may change the hemodynamic status of the patient including pulse rate, respiratory rate, blood pressure and urine volume. The change of hemodynamic status depends on the severity of blood loss.[6] TKA is a major orthopedic operation for advanced stage osteoarthritis of the knee. Increased average age of the patients leads to faster and more severe changes in hemodynamic status. According to advanced traumatic life support (ATLS) classification of hypovolemic shock by American college of surgeons, a blood loss of less than 750 ml (class I) does not require a blood transfusion. When we know the factors related to blood loss, we can adjust the protocol to reduce blood loss. Decreased blood loss and no blood transfusion will reduce operation costs and morbidity and mortality of patients. The results of multiple regression analysis showed four factors influencing blood loss after TKA, that is, radivac drain, tranexamic acid, postoperative pain score and BMI. Interestingly, using a radivac drain was related to increased blood loss. Kumar et al. showed that the routine use of suction drainage should be avoided after an uncomplicated total joint arthroplasty because it did not influence the incidence of wound complications and postoperative rehabilitation, thus helping to cut expenses.[9] Walmsley et al. showed a lower rate of transfusion at 7% among patients not using drains.[10, 11] The American Academy of Orthopedic Surgeons (AAOS) revealed strong evidence supporting not using a drain

with TKA due to no difference in complications or outcomes. The AAOS reviewed four high quality studies and three moderate quality studies, revealing no difference in multiple measures including VTE, infection, swelling, blood transfusions, hematoma formation, range of motion, length of stay, pain or reoperation between the treatment groups. Two high quality studies reported significantly higher transfusion rates among patients who received a drain. [20, 21] Total blood loss derives from visible and invisible blood loss. Visible blood loss is observed during the intraoperative period and during the postoperative period, the suction drain accounts for approximately one half of the total blood loss of each patient calculated by formula.[4] Invisible blood loss derives from hemolysis, blood permeating into interstitial fluid and concealed blood in the intraarticular space. Wound closure without that radivac drain will conceal the created tamponade effect of the joint leading to reduced blood loss.

Many research studies have recommended the routine use of intravenous tranexamic acid to reduce intraoperative and postoperative blood loss after joint arthroplasty. Wind et al. reviewed 2,269 consecutive primary TKA among 2,069 patients over a 3.5 year period and found that tranexamic acid infusion demonstrated a significant decrease in blood transfusions (p=0.01).(14) The transfusion rate without tranexamic acid was 6.5% (120/1839) but only 0.3% (1/330) with tranexamic infusion. Our data also showed a similar result.

Paul Hegarty et al. retrospectively studied 403 patients in relation to postoperative VAS and calculated blood loss using Gross' formula revealing no significant association.[16] However, Guay et al. found a significant correlation between measured blood loss and morphine consumption from 12 to 18 hours postoperative.[15] Our study found that 48 hours and more postoperative, VAS was related to increasing blood loss. As we know, TKA is an operation with blood loss from bone cut and soft tissue trauma. More soft tissue trauma creates more blood loss and interstitial blood accumulation, resulting in greater postoperative pain. Less pain causes increasing ability for the early range of motion exercise and ambulation, so less soft tissue swelling leads to less pain postoperatively.

Hrnack SA et al. retrospectively studied 94 TKA and 78 (total hip arthroplasty) THA cases, examining the effect of BMI, operative time (length of procedure) and anesthesia time on total blood loss. During primary TKA and primary THA obesity did not correlate with increased intraoperative blood loss.[17] Marlin S Carling et al. studied 114 unilateral hip arthroplasty and 79 unilateral knee arthroplasty patients in a prospective observational study, calculating blood loss using Brecher's formula. Multivariate regression analysis revealed low BMI and high preoperative Hb increased the risk of excessive bleeding among knee patients, and long operation time, increased the risk of RBC transfusion.[19]

Francisco Mesa-Ramos conducted a prospective randomized study of 121 TKA also showing no correlation with BMI concerning blood transfusion after TKA.[18] Our results showed that low BMI was related to increased blood loss which agreed with the study of Carling.[19]

The results of the study of Marlin S Carling et al. showed that long operative time increased the risk of RBC transfusion. In addition, a higher degree of intraoperative bleeding may extend surgical time and long operative time may increase bleeding over time.[19] Our results showed no correlation between the operative time and calculated blood loss among TKA patients using both Pearson's correlation and multiple regression analysis. About 63% of our patients completed operation within 60-90 minutes under a single experience surgeon. The surgical technique might directly affect both operative time and blood loss as already discussed. A skillful surgical technique would reduce operative time, soft tissue trauma and blood loss.

Theoretically, postoperative compression dressing, modified Robert Jones bandage, can cause the tamponade effect that reduces soft tissue edema and postoperative bleeding after TKA. Pinsornsak P. et al. conducted a prospective randomized controlled trial of 60 knees in over eight months revealing no differences in mean postoperative blood loss between groups.[22] We discontinued using the modified Robert Jones bandage in 2012. The result from this study showed the relation of the modified Robert Jones bandage with increased blood loss revealed by Pearson's correlation and no correlation using multiple regression analysis. The results indicate no benefit of using the modified Robert Jones bandage with TKA.

Conclusion

Using Pearson's correlation, a radivac drain, patellar resurfacing, modified Robert Jones bandage and higher postoperative pain score were related to increased blood loss after TKA. Using a radivac drain was also related to increased blood loss according to multiple regression analysis. Routine use of intravenous tranexamic acid related to reduced blood loss in TKA. BMI also was related to blood loss, and patients with low BMI may need greater awareness. Increased postoperative pain score related to increased blood loss, experience of surgeon, good surgical technique and postoperative pain control were important factors in this study. Identification of risk factors will help create greater awareness of high risk patients and improve intraoperative and postoperative protocols to minimize blood loss and transfusion associated risks for patients undergoing TKA.

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THE EFFECT OF A TOURNIQUET ON INTRAOPERATIVE SOFT TISSUE BALANCE IN COMPUTER-ASSISTED SURGERY IN TOTAL KNEE ARTHROPLASTY

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Abstract

Background: Achieving appropriate soft tissue balancing and accurate alignment is an essential procedure in total knee arthroplasty (TKA). Gap balancing affects the final knee kinematics and inadequate correction of soft tissue imbalances is considered an important factor for early TKA failure. During TKA, tourniquets are widely used to provide clear visualization of the tissue. The aim of the present study was to evaluate the effect of a tourniquet on intraoperative soft tissue balance in computer-assisted surgery (CAS) in TKA.

Methods: In this prospective cohort study, patients aged between 50 and 75 years were scheduled for primary CAS TKA due to osteoarthritis. Thirty knees operated by TKA using a navigation-assisted system (KICK system, DuPuy) were evaluated regarding soft tissue tension and compared between the tourniquet released and the tourniquet inflated in full extension (0°) and at 90° knee flexion.

Results: In total, 30 consecutive patients undergoing CAS TKA met the inclusion criteria. Differences were not significant in terms of soft tissue tension in knee full extension medial side (p=0.616), knee, full extension lateral side (p=0.780), 90° knee flexion medial side (p=0.573) and 90° knee flexion lateral side (p=0.163).

Conclusion: Our preliminary results showed that tourniquet application during CAS TKA did not significantly affect the soft tissue balance.

Keywords : Tourniquet, Intraoperative soft tissue balance, Computer-assisted surgery, Total knee arthroplasty

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Introduction

Achieving appropriate soft tissue balance and accurate alignment is an essential procedure in total knee arthroplasty (TKA).[1-3] Gap balance affects the final knee kinematics, and inadequate correction of soft tissue imbalances is considered an important factor for early TKA failure. The navigation systems are known to provide excellent restoration of the mechanical axis and precise component positioning, which also improves the accuracy of the balancing procedure by more objective and quantitative measures of flexion and extension gaps.[4, 5] The Joint Stability Graph in the navigation system provides the capacity to assess joint stability and manage gap balancing in TKA. This system continuously calculates the resulting joint gaps based on the maximum knee joint mobility and 3D implant geometries. During TKA, tourniquets are widely used to provide clear visualization of the tissue. One advantage of tourniquet use is reduced intraoperative blood loss.[6, 7] When surgeons use the tourniquet in performing TKA, they assess and adjust the soft tissue tension to achieve the balance of soft tissue both of the flexion and extension gaps. However, after finishing the surgery, the surgeons disconnect the tourniquet and let the patients move their knee via soft tissue tension without the tourniquet condition. When the author performed TKA with the navigation system, some differences in soft tissue tension measurement between the inflated tourniquet and deflated tourniquet were observed. , Any significant difference in terms of the soft tissue tension measurement when using the tourniquet has yet to be investigated. The aim of the present study was to evaluate the effect of a tourniquet on intra-operative soft tissue balance comparing between with and without tourniquet using a navigation system.

Methods

This study was approved by the institutional review board, the Royal Thai Army Medical Department. Consent to participate in this research was obtained from all patients. Thirty consecutive patients (20 women and 10 men), treated from August 2016 to August 2017, were included in this prospective cohort study. Patients were eligible for inclusion when they were scheduled for primary computer-assisted surgery (CAS) TKA due to osteo-arthritis, age between 50 and 75 years. Exclusion criteria comprised severe cardiac complaints, severe pulmonary disorders, Body Mass Index (BMI) >35 or severe coagulation disorder. Thirty knees operated by TKA using a navigation-assisted system (KICK system, DuPuy, Warsaw, Ind.) evaluated soft tissue tension and compared between tourniquet released and the tourniquet inflated in full extension (0°) and at 90° knee flexion. The medial parapatellar approach was used in all cases. The first pin was placed, and the distance measured using the 2-Pin X-Press Bone Fixator to place the second pin. The two pins (3 mm) were fixed in the tibia. A drill guide was used on the pins to avoid any disruption to the soft tissue. The 2-Pin X-Press Bone Fixator was placed on the pins and secured firmly in place with the locking screw. The two holes were made on the array block point distally, with the notch towards the patient. The pin position was marked on the femur and a stab incision was made through the soft tissue using a scalpel. Using the 2-Pin X-Press Bone Fixator, the pins were drilled in the bone bicortically. The 2-Pin X-Press Bone Fixator was used with 4 mm pins. The final position was adjusted to ensure a clear line of sight between the array and the camera. Tightening of the array was performed using an adjustment screw. The surgeon started registration of the femoral head center by rotating the leg in the hip joint in a circular manner. The landmarks of the femur and the tibia were registered by pointer For the femur these comprised the distal mechanical axis point, epicondylar axis, Whiteside's line, medial condyle lateral condyle, anterior reference point while the tibia comprised the proximal mechanical axis point, tibia anterior-posterior direction, medial plateau, lateral plateau and malleoli. After the tourniquet was released the surgeon moved the leg from full extension to full flexion to create the joint stability graph. The joint stability graph showed two curves for the medial and the lateral gap between the femur and tibia implants over the leg's flexion range. The data from the joint stability graph were collected (full extension: medial and lateral side, flexion 90 degree: medial and lateral side). Next, the tourniquet was inflated and the surgeon moved the leg from full extension to full flexion then collected the data from the joint stability graph. Statistical analysis was performed using the paired *t*-test to compare the soft tissue tension between inflated tourniquet

and released tourniquet in knee extension 0 degrees (medial side and lateral side) and knee flexion 90 degrees (medial side and lateral side). The level of significance was set at p <0.05.

Picture 1. Joint stability graph

Results

In total, 30 consecutive patients undergoing CAS TKA met the inclusion criteria. The mean age of patients was 69.7±5.5 years (range 58-81 years) and mean BMI of the patients was 25.0±2.4 kg/m^2 (range 18.9-30.1 kg/m^2). Differences were noted but without significance between the with and without tourniquet groups in terms of soft tissue tension i.e., in knee full extension medial side 4.40±3.2 vs. 4.48±3.35 (p=0.616), knee full extension lateral side 10.33±2.25 vs. 10.27±2.46 (p=0.780), 90° knee flexion medial side 5.28±3.63 vs. 5.22±3.60 (p=0.573) and 90° knee flexion lateral side 8.37±4.12 vs. 8.67±4.60 (p=0.163).

Table1. Effect on knee extension with and without tourniquet

	without tourniquet Mean±SD	with tourniquet Mean±SD	t	df	p-value
Extension					
Medial	4.40±3.24	4.48±3.35	-0.507	29	0.616
Lateral	10.33±2.25	10.27±2.46	0.281	29	0.780
Flexion					
Medial	5.28±3.63	5.22±3.60	0.571	29	0.573
Lateral	8.37±4.12	8.67±4.60	-1.430	29	0.163

Paired t-test

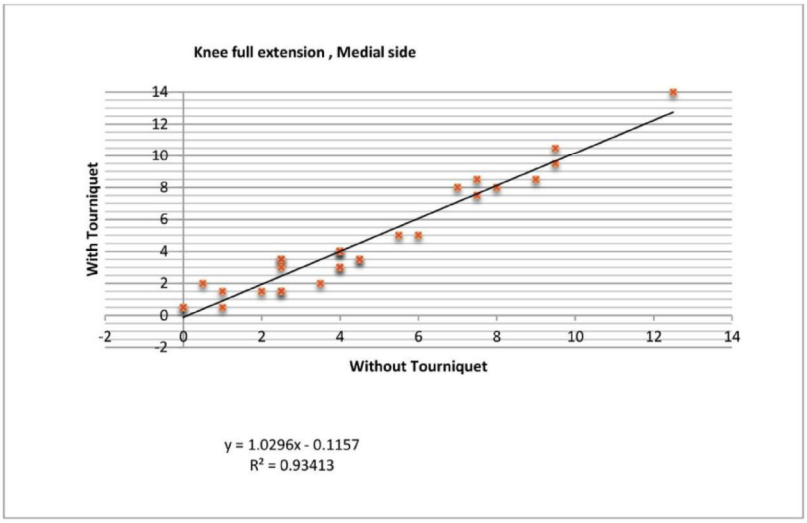

Fig 1. Soft tissue tension in knee full extension with and without tourniquet, medial side

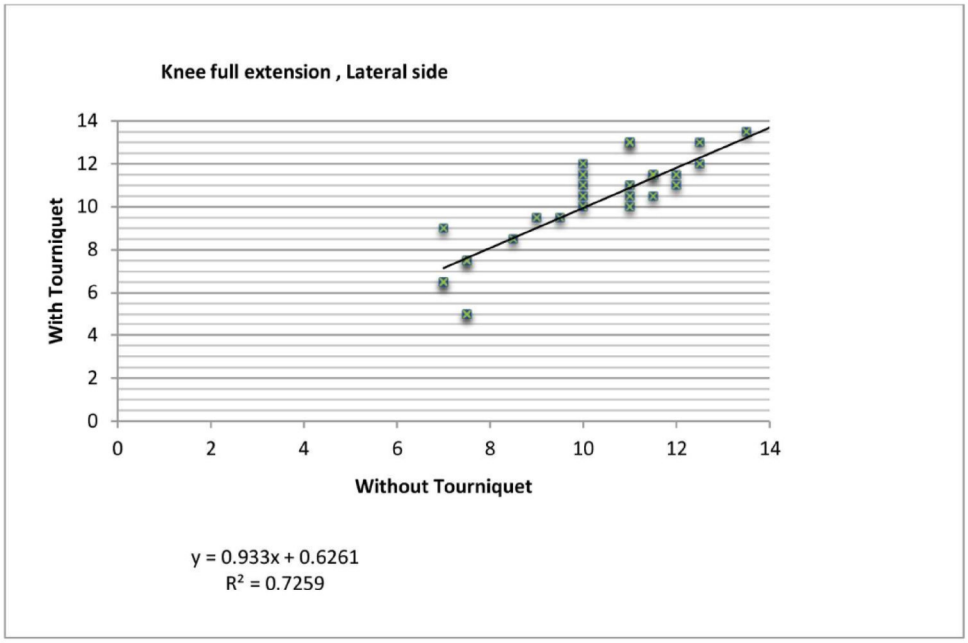

Fig 2. Soft tissue tension in knee full extension with and without tourniquet, lateral side

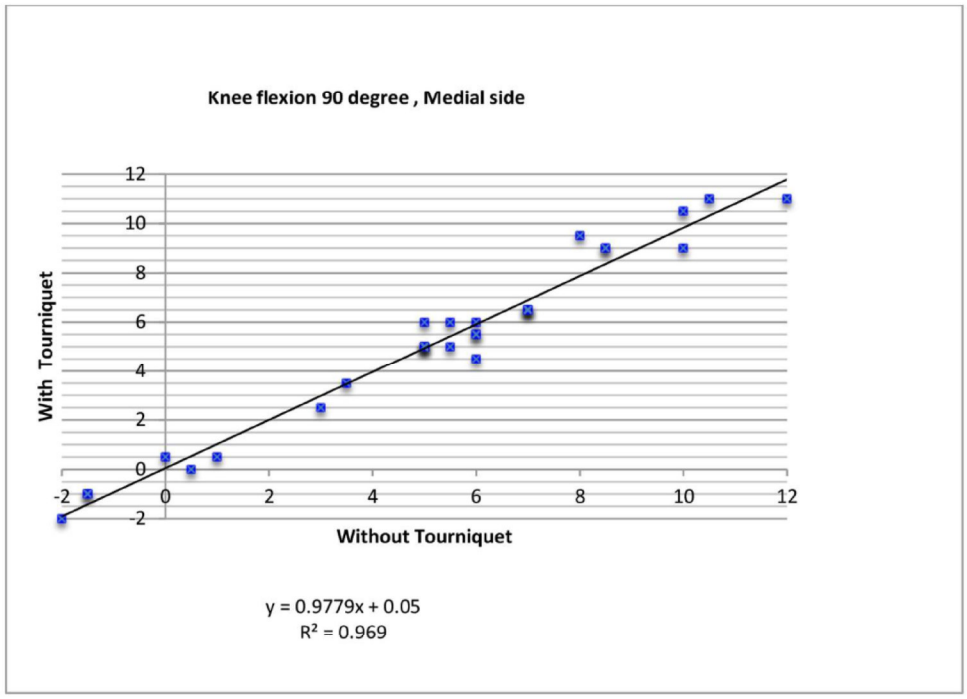

Fig 3. Soft tissue tension with and without tourniquet in knee flexion 90 degree, medial side

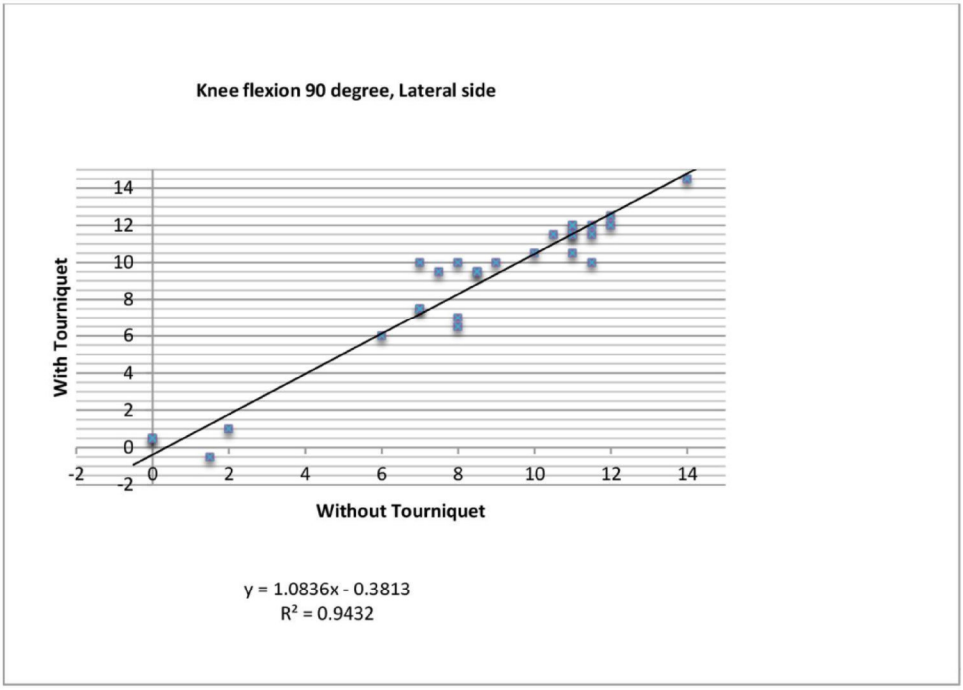

Fig 4. Soft tissue tension with and without tourniquet in knee flexion 90 degree, lateral side

Discussion

Successful outcomes of TKA depend on accurate implant position, restoration of limb alignment and optimal gap balancing.[8] Malpositioning of the femoral or tibial component can lead to early loosening, increased polyethylene wear and poor patellar tracking.[9] Gap balancing affects the final knee kinematics, and inadequate correction of soft tissue imbalances is considered an important factor for early TKA failure.[10,11] The soft tissue imbalance may be present in the form of instability, deformity, contracture or a combination of these elements. The importance of obtaining proper soft tissue balance at the time of TKA is well recognized,[12] and numerous techniques have been described to correct imbalances, including varus and valgus deformities, flexion contractures, recurvatum and bone deficiencies.[12,13]

As the incidence of TKA continues to increase, it becomes important to develop techniques to improve outcomes while simultaneously minimizing the incidence of revision. A common difficulty associated with manually performed TKAs is obtaining accurate intra-operative soft tissue balancing, an aspect of this procedure that surgeons traditionally address through their feel and experience. This remains so despite the availability of several devices designed to assist in this regard, including tensors, [14-17] spacers [17] and electric instruments. [18-21] Regarding navigation systems, the joint stability graph shows two curves for the medial and the lateral gap between the femur and tibia implants over the leg's flexion range and show a number after measuring the soft tissue tension simultaneously. Because the soft tissue tension is measurable, it should not be manipulated by any other factors. The effect of the tourniquet when inflated during surgery is the suspected factor and proved by the results in this proposal.

This is the first study to evaluate the relationship between tourniquet use and the possible influences on soft tissue tension measurement using a navigation system. From the results, tourniquet application during CAS TKA did not significantly affect the soft tissue tension measurement.

However, limitations of this study should be noted. First of all, the sample size was relatively small. Larger series are needed to confirm the effect of the tourniquet on intra-operative soft tissue tension measurement. Second, the author created the joint stability graph using bone to bone contact, i.e., distal femur and proximal tibia, instead of using an injoint spreader to avoid creating any error in the data resulting from the movement of an injoint spreader. It could be better if a stable injoint spreader was used to compare the soft tissue tension.

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CORNEAL ENDOTHELIAL CELL CHANGES IN THE EYES OF PRIMARY ANGLE CLOSURE SUSPECTS TREATED USING LASER PERIPHERAL IRIDOTOMY COMPARED WITH UNTREATED FELLOW EYES AT PHRAMONGKUTKLAO HOSPITAL

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Abstract

Objectives: The study's primary outcome was to compare corneal endothelial cell changes in the eyes of Primary Angle Closure Suspects (PACS) treated by laser peripheral iridotomy (LPI) and in untreated fellow eyes. The secondary outcome was to assess short-term effects of LPI on the corneal endothelium among PACS.

Study design: The study employed a prospective design.

Methods: PACS visiting Phramongkutklao Hospital were enrolled in the study. Data were collected regarding type and setting of laser parameters, endothelial cell counts and morphology, gonioscopy and underlying diseases. Randomized eyes were treated using LPI while the other eye was treated by LPI 3 months later. Rate of corneal endothelium loss in the treated eyes were assessed and compared with untreated fellow eyes. Primary outcome was interpreted by pair *t*-test while secondary outcome was interpreted using the ANOVA test.

Results: A total of 31 PACS (62 eyes)were included in the study. The median age was 67 years (range 43-90). PACS totaled 21 females (67.7%) and 10 males (32.3%). The mean total power of double frequency Nd:YAG (532 nm) laser and Nd:YAG laser, were 855.6±53.9 mW and 2.3±0.5 mJ, respectively. Concerning primary outcomes, the mean corneal endothelial cell density before LPI and postLPI 3 month was 2608.5±399.8 and 2605.6±397, respectively, 1 cell/mm^2. In untreated fellow eyes, the mean corneal endothelial cell density at 1 and 3 months was 2607.1±419.6 and 2605.0±403.2 cell/mm^2, respectively. No significance was found in rate of endothelial cell change between treated and untreated fellow eyes using LPI (p=0.981). Regarding secondary outcomes, corneal endothelial cell density did not decrease significantly in 3 months (p=0.126).

Conclusion: No difference was observed in corneal endothelial cell changes between treated and untreated fellow eyes using LPI over 3 months. LPI did not affect corneal endothelial cell loss in a short term period.

Keywords : Corneal endothelial cell, Primary angle closure, Laser peripheral iridotomy

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Introduction

Angle closure glaucoma is more common in Asia than in Europe and Africa.[1] The results of glaucoma research in the Romklao Community in Bangkok showed that one-seventh of 701 subjects, older than 50 years, could have angle closure glaucoma and this risk runs to women three times more than men.[2] Laser peripheral iridotomy (LPI) is the first line of treatment for this disease.[3] LPI can be performed using a neodymium (Nd):YAG laser leading to photodisruption against target tissue and the argon laser, which causes a photothermal effect against the target tissue.[3,4]

The sequential laser technique combines these two types of lasers for treatment and is more popular because they produce good results and low complication rate. Complications of LPI include corneal decompensation, bullous keratopathy.[5,11] Other complications include transient intraocular pressure rising, anterior uveitis, closure by iridotomy, hyphema, cataract formation, retinal injuries, malignant glaucoma and monocular blurring.[3]

The purpose of this study was to compare corneal endothelial cell changes in the eyes of primary angle closure suspects (PACS) treated using LPI and in untreated fellow eyes in Phramongkutklao Hospital. The secondary outcome was to assess short term effects of LPI on corneal endothelium among PACS.

Methods

The study employed a prospective design regarding PACS at Phramongkutklao Hospital. All subjects met the inclusion criteria and were listed for elective primary LPI. The inclusion criteria were patients aged more than 18 years having a diagnosis of PACS. Appositional closure was more than 180o by gonioscopy (Modified Shaffer grading), intraocular pressure (IOP) ≤21 mmHg and no peripheral anterior synechiae (PAS). Subjects were excluded when a history was reported of corneal dystrophy/ degeneration, uveitis, iritis, endopthalmitis, intraocular laser, surgery or trauma, poor compliance or loss follow up, pregnancy or allergy to anesthetic drug. Subjects were evaluated for eligibility and baseline data at the Ophthalmology Department, Phramongkutklao Hospital.

All subjects were examined using a slit lamp and gonioscope. IOP was measured by Goldmann applanation tonometer. Central corneal endothelial cells were measured using a noncontact specular microscope. PACS were randomized to be treated using sequential LPI in one eye. Data were collected including type and setting of laser parameters, post LPI IOP, central corneal endothelial cells, central corneal thickness, coefficient variation and hexagonality of corneal endothelial cells at one, two and three months after LPI. The other eye was treated using LPI three months later. The primary outcome was assessing the short term rate of corneal endothelial cell loss in the treated eye compared with that of untreated fellow eyes. The secondary outcome was assessing the short term effects of LPI on corneal endothelial cell loss. The study was approved by the Institutional Review Board of the Royal Thai Army Medical Department. Informed consent was obtained from all subjects.

Sample size and power

The formula for calculating sample size in the present study is shown below.

$$n = \frac{(Z_\alpha + Z_\beta)^2 S^2}{d^2}$$

$$\frac{(1.96 + 1.28)^2 17161}{86.51^2}$$

$$= 24.07 \sim 25 \text{ subjects}$$

- Confidence interval 95%, $\alpha = 0.05$ $Z_\alpha = 1.96$
- Power 90%, $Z_\beta = 1.28$
- $S^2 = 17161$
- d = μ_1-μ_2= 86.51

Statistical Analysis

General demographic data were described using mean, median and percentage. Corneal endothelial cell loss between eyes treated using LPI and untreated fellow eyes were compared by the paired *t*-test. Secondary outcome was interpreted using the ANOVA test. Statistical analysis was performed using Stata 11, and *p*-values of <0.05 were considered statistically significant.

Results

Thirty-five subjects (70 eyes) met the eligibility criteria,

and 4 subjects were lost to follow-up after LPI. The remaining 31 PACS (62 eyes) completed the study. The mean follow-up period totaled 3.3 months. The mean age was 67 years (range 43-90). Subjects comprised 21 females (67.7%), and 10 males (32.3%) including 11 subjects with diabetic mellitus (35.5%), 16 subjects with hypertension (51.6%) and 10 subjects with dyslipidemia (32.3%).

Table 1. Patients' demographic data

Age Mean±SD (Min-Max)	67.2±11.3(43-90)
Gender	**Number (%)**
Male	10 (32.3)
Female	21 (67.7)
Underling disease	
Diabetic mellitus	11 (35.5)
Hypertension	16 (51.6)
Dyslipidemia	10(32.3)
Type of angle closure	
PACS	31 (100)

Laser energy use in LPI is shown in **Table 2**. Mean total energy of double-frequency Nd:YAG (532) laser, and Nd:YAG laser in first treated eye were 855.6±53.9 mW, and 2.3±0.5 Joules (J), respectively. Mean total energy of double-frequency Nd:YAG (532) lasers, and Nd:YAG laser in the other treated eye were 857.3±56 mW, and 2.3±0.4 J, respectively.

Table 2. Laser energy use in laser peripheral iridotomy

	Total energy (mean±SD)	**Range of energy** (min - max)
Treatment I		
Double-frequency	855.6±53.9 mW	800-950 mW
Nd:YAG	(0.86±0.05 J/sec)	(0.8-0.95 J/sec)
Nd:YAG laser	2.3±0.5 mJ	1.2-3 mJ
Treatment II		
Double-frequency	857.3±56 mW	800-950 mW
Nd:YAG	(0.86±0.06 J/sec)	(0.8-0.95 J/sec)
Nd:YAG laser	2.3±0.4 mJ	1.5-2.9 mJ

Ocular parameters with LPI treated and untreated eyes are shown in **Table 3**. The mean rate of corneal endothelial cell change between treated and untreated eyes at three months revealed no statistical significance (p=0.981).

Table 3. Ocular parameters with pre- and postlaser peripheral iridotomy at 3 months

	Pre – LPI (mean±SD)	**Post – LPI 3 months** (mean±SD)	***p*-value**
IOP(mmHg)			
Treated eye	15.5±3.1	14.6±2.5	0.198
Untreaed eye	15.5±2.9	15.1±2.8	
ECD(cell/mm2)			
Treated eye	2608.5±399.8	2605.6±397.1	0.981
Untreaed eye	2607.1±419.6	2605.0±403.2	
CCT(μm)			
Treated eye	537.5±40.2	535.1±40.2	0.072
Untreaed eye	533.8±40.1	530±41.8	
C.V.(%)			
Treated eye	40.5±7.1	40.6±7.2	0.094
Untreaed eye	38.4±6.6	38.7±6.5	
Hexagonality(%)			
Treated eye	51.7±8.9	51.7±8.5	0.886
Untreaed eye	52.3±8.3	52±7.9	

a Paired t-test

LPI = laser peripheral iridotomy, IOP = intraocular pressure, A/C depth = anterior chamber depth, ECD = Corneal endothelial cell density, CCT = Central corneal thickness, C.V. = coefficient variation in size of corneal endothelial cell

Mean corneal endothelial cell density after LPI is shown in **Table 4** and indicating that corneal endothelial cell density did not decrease significantly over three months (p=0.126)

Table 4. Ocular parameters with pre- and post-laser peripheral iridotomy

	Pre - LPI (mean±SD)	Post – LPI 3 months (mean±SD)	Parameter Change (mean±SD)	p-value
IOP(mmHg)	15.5±3.1	14.6±2.5	3.3±2.1	0.544
ECD(cell/mm^2)	2608.5±399.8	2605.6±397.1	13.6±15	0.126
CCT(μm)	537.5±40.2	535.1±40.2	13.2±10	0.178
C.V.(%)	40.5±7.1	40.6±7.2	4.7±4.2	0.556
Hexagonality(%)	51.7±8.9	51.7±8.5	8.9±7.2	0.206

Discussion

This study compared corneal endothelial cell changes in the eyes of PACS treated by LPI and in untreated fellow eyes showing the short term effects of LPI. The mean rate of corneal endothelial cell change between treated and untreated eyes at three months revealed no significance (p=0.981). Regarding the secondary objective, corneal endothelial cell density did not decrease significantly over three months (p=0.126). The results were similar to related studies. Jess Smith's study[5] showed corneal endothelial loss of 125 cell/mm^2 after argon LPI (p=0.09) while Shiu-Chen Wu's[7] study showed significant corneal endothelial cell loss within one year after LPI but without significance at three months (p=0.467). However, William C. Panek's study [8] demonstrated significant corneal endothelial cell loss of 95 cells/mm^2 among subjects with occludable angles at the treated site after Nd:YAG LPI (p=0.04). many studies have shown the effect of laser treatment concerning the corneal endothelium depending on pre-existing corneal disease [5], total energy use[6] and type of laser.[6, 9, 11]

Jess Smith and Peter Whitted [5] showed corneal endothelial loss if 812 cells/mm^2 after argon LPI among patients who had pre-existing Fuchs' dystrophy and corneal edema. However, pre-existing corneal diseases were excluded in the present study and no corneal edema was found among all subjects.

The mean total energy of LPI in the present study was lower than related studies [6, 11] (**Table 2**). Tony Ho and Richard Fan[11] showed the long term effects of sequential argon-YAG LPI in dark irides and reported the total amount of energy in argon and Nd:YAG lasers was 3.6 J and 9.4 mJ, respectively. The procedures were safer involving fewer complications than argon or YAG laser alone. In addition, Wilhelmus RK[6] reviewed five case reports of corneal edema after high energy of argon laser LPI reporting 63, 48.5, 7, 25, and 25 J.

The advantage of the present study was the aged-match control group of LPI concerning corneal endothelial cell loss. The present study was limited by the small sample size, reproducibility of ocular parameter measurements and

short term follow-up period. Research in a larger population including long term effects on corneal endothelial cell change are necessary for further investigation.

Conclusion

No difference was observed regarding corneal endothelial cell changes between treated and untreated fellow eyes using LPI at three months. LPI did not affect corneal endothelial cell loss over a short term period.

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EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS ON HEMOGLOBIN LEVELS AMONG PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE: A RANDOMIZED CONTROL TRIAL

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Abstract

Background: Anemia commonly occurs among patients with advanced stage chronic kidney disease (CKD) and has been associated with poor clinical outcomes. The role of angiotensin converting enzyme (ACE) inhibitors in aggravating the anemia of patients with CKD is controversial.

Objective: The study aimed to evaluate the effect of ACE inhibitors on hemoglobin levels among patients with advanced CKD.

Methods: Twenty-two patients with CKD stages IV or V and presenting stable hemoglobin levels over 12 weeks were randomly assigned either to receive enalapril (N=10) or amlodipine (N=12) among those whose blood pressure was controlled with antihypertensives other than ACE inhibitors. Hemoglobin levels were monitored at 8 and 16 weeks after treatment.

Results: Clinical characteristics were similar at baseline between the enalapril- and amlodipine-treated groups, and no difference was observed in blood pressure control during follow-up. Enalapril exhibited no significant change in hemoglobin levels from 11.1 g/dL (the interquartile range or IQR 11.1 to 11.5) at baseline to 11.4 g/dL (IQR 10 to 12) at 8 weeks and 10.7 g/dL (IQR 9.9 to 11.8) at 16 weeks of treatment. Hemoglobin levels during the 16-week follow-up declined on average by -0.3 g/dL (IQR -0.9 to 0.4) per 16 weeks in the enalapril group and by -0.1 g/dL (IQR-0.7 to 0.4) per 16 weeks in the amlodipine group (p=0.868).

Conclusion: Administration of ACE inhibitors on blood pressure control was not associated with declining hemoglobin levels among patients with advanced CKD. Additional studies are necessary to confirm this result.

Keywords : Anemia, ACE inhibitors, Chronic kidney disease

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Introduction

Anemia is a common complication of chronic kidney disease (CKD) and is associated with reduced functional status and quality of life, left ventricular dysfunction, congestive heart failure and adverse clinical outcomes.[1, 2] Early identification and treatment of anemia may improve cardiovascular morbidity and mortality. Resistance to recombinant human erythropoietin (EPO) therapy among patients with CKD involves multifactorial etiologies including erythropoietin insufficiency, iron deficiency, inadequate dialysis, bone marrow disease, hemolysis, secondary hyperparathyroidism and use of renin angiotensin aldosterone system (RAAS) inhibitors.[3]

Anemia has been reported as a side-effect of RAAS inhibitors among healthy subjects and patients with essential hypertension, congestive heart failure and renal transplant recipients.[4-8] Additionally, angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) have been linked to reducing response to EPO administration and developing resistant anemia in dialysis.[9-12] Its pathogenesis is multifactorial and may include inhibiting endogenous EPO production, producing an erythropoiesis-inhibiting protein and inhibiting angiotensin II mediated stimulation of erythrocyte precursors.[13,14] Also, data is limited regarding evaluating the effect of ACEI on renal anemia patients with late stage CKD.[5,16] Consequently, no definitive conclusion has been reached concerning the role of ACEI in treating anemia especially among patients with advanced stage CKD. The present study was designed to test the hypothesis regarding administering enalapril to decrease hemoglobin and hematocrit levels among patients with advanced CKD compared with other standard antihypertensive agents.

Methods

This 16-week prospective randomized single blind study was conducted among patients with CKD stages IV to V at the outpatient clinic, Phramongkutklao Hospital. The study was approved by the Institutional Review Board of Phramongkutklao Hospital. Recruitment began August 2014 and was completed January 2015.

Subjects

The inclusion criteria of the study comprised age 18 years or older, CKD stages IV or V and more than 12 weeks with a hemoglobin concentration <12 g/dL among females and <13 g/dL among males. All subjects received stable treatment with antihypertensive agents, lipid lowering agents and metabolic controls for at least 12 weeks and received no treatment with RAAS inhibitors or recombinant human EPO therapy within 12 weeks before starting the study.

Patients with other causes of renal anemia were excluded from the study, i.e., vitamin deficiency, iron deficiency, chronic blood loss, hemolysis or bone marrow disease, hyperkalemia, active malignancy, severe heart, lung or liver disease, stroke, chronic infection, pregnancy, any immunological or inflammatory disorders and known history of enalapril hypersensitivity. All patients provided informed written consent and were questioned to assure that dietary intake and daily lifestyle did not change during follow-up.

Intervention

Eligible patients were randomly assigned to two groups. One group ingested enalapril (N=10), 5 to 20 mg orally daily keeping blood pressure <140/90 mmHg for 16 weeks. The other group ingested amlodipine (N=12), in a similar manner. When maximal doses (20 mg/day for enalapril or 20 mg/day for amlodipine) of initial medications were reached, beta or alpha blocker was added to control high blood pressure more adequately. Adherence was monitored by pill count during each visit.

Clinical and Laboratory Monitoring

Medical history and physical examination were performed for each subject at the outpatient clinic. Casual systolic and diastolic BP were measured using a standard mercury sphygmomanometer applied on the same arm after a 10-minute rest in a sitting position.

After an 8-hour overnight fast, all patients underwent routine laboratory tests including assays for plasma levels of hematocrit, hemoglobin, potassium, creatinine and estimated glomerular filtration rate (GFR) using the 2009 CKD-EPI creatinine equation and staging according to, "The Kidney Disease: Improving Global Outcomes (KDIGO) 2012" at baseline and at the end of the study.

Adverse events that were or were not considered to be related to enalapril treatment were monitored every four weeks.

The patients were questioned in a systematic way about their experiences concerning any adverse events during the previous four weeks. Patients also underwent blood drawing for safety tests including complete blood count and liver function tests. For serious adverse events, enalapril therapy was discontinued at once and the study was terminated.

Statistical Analysis

Measured values of the results were expressed in median with interquartile range (IQR) and percentage. Wilcoxon signed ranks test was used to compare the change of parameters within group at baseline, 8 weeks and 16 weeks. Parameters were compared between groups at baseline, 8 weeks and 16 weeks using the Chi-square, Mann-Whitney and Fischer's exact tests. Statistical analyses were performed using SPSS, Version 15, for Windows (SPSS Inc, Chicago, IL, USA). A p <0.05 was considered statistically significant.

Results

A total of 42 patients with CKD stages IV to V were screened for possible study enrollment. Twenty-two patients were eligible according to the entry criteria and received enalapril or amlodipine treatment. All patients were 100% adherent to the medication prescription based on pill count and average enalapril dose was 20 mg/day. Mean age was 70.2 years (IQR 61.5-76.2) and mean estimated GFR was 12.4 mL/min/1.73 m^2 (IQR 7.3-24.7). Underlying diseases included hypertension (95%), dyslipidemia (59%), type 2 diabetes (54.5%) and coronary heart disease (22.7%). Characteristics of the patients are shown in **Table 1**. No significant differences were found in age, sex, comorbid diseases, renal function, hemoglobin, hematocrit and iron status.

Table 1. Characteristics of the study population

Variables	Amlodipine (N=12)	Enalapril (N=10)	p-value
Age (yrs)	69.5 (59 to 75.5)	71 (62 to 78)	0.716
Male (%)	5 (41.7%)	7 (70%)	0.231
Smoking (%)	4 (33%)	4 (40%)	1.000
Alcoholic drinking (%)	6 (50%)	4 (40%)	0.691
Underlying disease			
Hypertension	12 (100%)	9 (90%)	1.000
Dyslipidemia	10 (83.3%)	3 (30%)	0.624
Type 2 diabetes	7 (58.3%)	5 (50%)	0.375
Coronary heart disease	2 (16.7%)	3 (30%)	0.455
Serum creatinine (mg/dL)	3.46 (3.5 to 7.0)	3.55 (2.3 to 6.9)	0.262
Glomerular filtration rate (mL/min/1.73	8.7 (6.4 to 15.1)	15.5 (7.6 to 26.3)	0.114
Hemoglobin (g/dL)	10.4 (9.8 to 12.5)	11.1 (11.0 to 11.5)	0.164
Hematocrit (%)	31.6 (29.2 to 37.6)	34.0 (31.4 to 34.5)	0.339
Ferritin (ng/mL)	605.6 (177.2 to 792)	212 (129 to 383.8)	0.147
Transferrin saturation (%)	31.6 (29.9 to 37.4)	39.9 (37.3 to 42.6)	0.099

Data presented as median with IQR

Hematocrit and Hemoglobin Changes after Treatment

Baseline median hematocrit was 32.3% (IQR 29.7 to 35.9) and median hemoglobin was 10.6 g/dL (IQR 9.9 to 11.6). Enalapril showed no significant change in hemoglobin levels from 11.1 g/dL (IQR 11.1 to 11.5) at baseline to 11.4 g/dL (IQR 10 to 12) at 8 weeks and 10.7 g/dL (IQR 9.9 to 11.8) at 16 weeks of treatment (**Figure 1**). Hemoglobin levels during the 16-week follow-up declined on average by -0.3 g/dL (IQR -0.9 to 0.4) per 16 weeks in the enalapril group and by -0.1 (IQR-0.7 to 0.4) per 16 weeks in the amlodipine group (p=0.868), but did not reach statistical significance. Moreover, no significant difference was found in median changes in hematocrit and hemoglobin at 8 and 16 weeks between enalapril and amlodipine groups (**Table 2**).

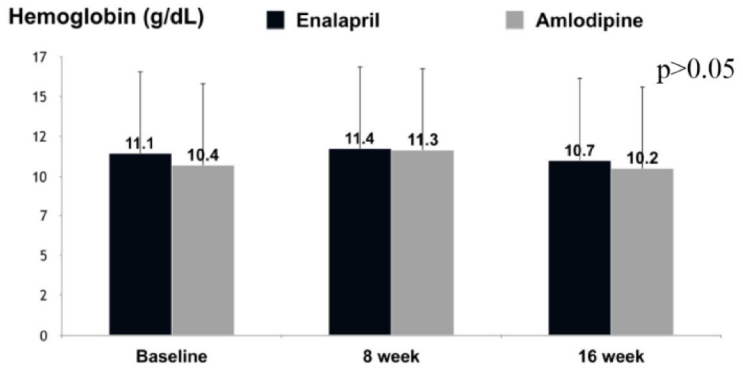

Fig 1. Median levels of hemoglobin after treatment with enalapril and amlodipine. No significant differences were found within and between groups regarding hemoglobin levels any time point (p >0.05).

Table 2. Median changes of hematocrit and hemoglobin after 8 and 16 weeks of treatment

Median changes	Amlodipine (N=12)	Enalapril (N=10)	p-value
Median changes at 8 weeks			
Hematocrit (%)	0.6 (-0.5 to 2.4)	-0.2 (-3.0 to 1.8)	0.356
Hemoglobin (g/dL)	0.1 (-0.2 to 0.6)	-0.2 (-0.9 to 0.5)	0.305
Median changes at 16 weeks			
Hematocrit (%)	-1.1 (-2.5 to 1.1)	-1.3 (-3.1 to 0.3)	0.509
Hemoglobin (g/dL)	-0.1 (-0.7 to 0.4)	-0.3 (-0.9 to 0.4)	0.868

Data presented as median with IQR

Safety Profiles

During the 16-week study period, one of the patients withdrew prematurely because of developing hyperkalemia after initiating enalapril treatment and hyperkalemia subsided upon drug withdrawal. No serious complications were observed and no patient received transfusion during the study.

Discussion

The present study constituted a prospective clinical trial of enalapril treatment concerning anemia status among patients with advanced CKD. Among patients with CKD stages IV to V, compared with baseline, the standard dose enalapril treatment presented a decreasing trend regarding hemoglobin and hematocrit, but without statistical significance. Thus, these findings indicated that antihypertensive treatment using ACEI for 16 weeks did not directly affect anemic status among patients with late stage CKD.

Our results did not demonstrate significant changes in hemoglobin after 16 weeks of enalapril treatment. In contrast, related retrospective and prospective studies have demonstrated that administering RAAS inhibitors lowered hemoglobin levels among patients with CKD undergoing dialysis., However, most reports focused on patients undergoing dialysis concerning recombinant human EPO therapy with high dose RAAS inhibitors or renal transplant recipients.[8-15] However, our study included patients with advanced CKD without dialysis and EPO treatment. Additionally, a large cohort study from Japan indicated that ACEI had no effect on recombinant human EPO therapy treatment concerning anemia among patients undergoing hemodialysis treated with a relatively low dose of ACEI and low-dose recombinant EPO.[17] Furthermore, a prospective, crossover study concerning ACEI treatment for four months among patients undergoing hemodialysis demonstrated that ACEI did not contribute to recombinant human EPO resistance among patients undergoing hemodialysis.[18] Therefore, the negative role of RAAS inhibitors may become more apparent only among dialysis patients receiving exogenous low dose recombinant human EPO treatment and high dose RAAS inhibitors.

Although our results did not demonstrate significant changes in hemoglobin after 16 weeks of treatment, administering enalapril tended to lower hemoglobin levels among patients with advanced stage CKD. Recently, a systemic review and meta-analysis was conducted in seven studies with 29,061 patients clearly indicating an association between anemia and the use of RAAS inhibitors.[19] The negative effect of ACEI on erythrocyte production may imply that ACE inhibitors alter the control of erythropoiesis with reduced sensitivity to EPO and directly inhibit erythropoiesis in vitro.[20,21] Moreover, ACEI also increased the plasma N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) levels at high levels that inhibited erythropoiesis and caused EPO resistance and renal function, essential to maintain low plasma AcSDKP levels.[14, 22, 23] Plasma AcSDKP concentration depended on residual renal function and dose of ACEI used. Thus, the negative results in our study stemmed from using an average dose of enalapril at 20 mg/day among patients with GFR at 12.4 mL/min/1.73 m^2.

This study had several limitations. First, the present study included a relatively small number of patients, but the data were all registered and analyzed in comparison with the control group for 16 weeks of treatment, and factors affecting erythropoiesis other than enalapril were excluded before and during the study. Secondly, short term studies should not imply that enalapril is without long term adverse effects on renal anemia because related studies have documented that patients treated with enalapril needed a higher dose of recombinant human EPO therapy than the control group over the one-year study period. Thirdly, we included major patients with mild anemia with an average hemoglobin level of 10.6 g/dL and without recombinant human EPO therapy, so any negative effects of enalapril on erythropoiesis may have not been detected.

Conclusion

In conclusion, our study did not demonstrate an association between anemia and the use of ACEI among patients with late stage CKD. The effect of ACEI on hemoglobin among patients with CKD should be further assessed using a larger number of patients with a high dose of RAAS inhibitors over a longer treatment period.

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