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A Patient with Post Infectious Immune Mediated Neuropathy (Miller Fisher Syndrome)

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Abstract

The Miller Fisher variant is an uncommon but well known syndrome being described as a triad of areflexia, ataxia and complex ophthalmoplegia. It is characterized by antibodies against myelin that affects peripheral nerves, extraocular muscles and Schwann cells. Anti-ganglioside antibodies have been recognized in disease pathogenesis and decreasing antibody production is the mainstay of treatment. The course is usually benign with improvement after immunomodulation. This case report describes the approach to a patient suspected of having a demyelinating disorder. It delineates the subsets of immune mediated neuropathies in evaluating the diagnosis and emphasizes the need for early therapeutic intervention in achieving a good clinical outcome.

Keywords

Miller Fisher, Anti-Ganglioside, Demyelinating, Immune Mediated

1. Introduction

Anti GQ1b antibodies target peripheral nerves, activate complement and cause conduction block. This leads to an immune mediated neuropathy affecting extraocular muscles. Miller Fisher syndrome (areflexia, ataxia and complex ophthalmoplegia) encompasses a spectrum of immune mediated motor and sensory neuropathies.

A 35-year-old female with a prior history of an upper respiratory tract infection presented with diplopia, bilateral orbital pain and headache. Clinical examination revealed an ataxic gait, areflexia and a complex ophthalmoplegia consistent with the clinical triad of Miller Fisher Syndrome.

The hallmark of this syndrome is the presence of anti GQ1b antibodies. This condition usually has an excellent prognosis with treatment as it usually follows an uncomplicated course without remissions. Treatment is based on reducing antibody levels.

2. Case Report

A 35-year-old woman presented with a two day history of diplopia, bi-frontal headache and bilateral orbital pain. Two weeks prior to these symptoms, she had a non-specific upper respiratory tract infection. There was no significant past medical history. Drug history included analgesics when necessary. The patient did not use alcohol, cigarettes or illicit drugs.

On examination she had a right sided ptosis and bilateral lateral rectus weakness. Other cranial nerves were normal. Diplopia was pronounced on bilateral horizontal gaze.

Tone and power were normal in the upper and lower limbs. Reflexes throughout were all absent and plantars were equivocal bilaterally. There was bilateral dysmetria but no dysdiadochokinesia. Gait was ataxic with inability to tandem walk. Position, vibration and pin prick sensation were all intact. Romberg's test was negative. Cardiovascular, respiratory and abdominal examinations were all unremarkable.

Investigations included the following: complete blood count, urea and electrolytes, liver enzymes and inflammatory markers were all within normal limits. The cerebrospinal fluid (CSF) protein was mildly elevated at 73 (12 - 60) mg/dl. The fluid was acellular with a normal glucose level. Electromyography (EMG)/nerve conduction study showed normal sensory action potentials. Small and splayed common peroneal compound muscle action potentials with normal nerve conduction velocities and normal F wave latencies were found. The findings were in keeping with bilateral common peroneal nerve dysfunction. Muscle sampling was normal. Computed Tomography (CT) brain (non contrast) was normal. Magnetic Resonance Imaging (MRI) brain non contrast was normal. Anti GQ1b Ig G was elevated, >1:100 (Negative-<1:100).

Treatment was initiated with intravenous Immunoglobulin (IVIG) 0.4 grams/kilogram/day for 5 days. There was significant clinical improvement during the hospital stay. However at six weeks the patient still exhibited an ataxic gait and a further course of IVIG was given at 0.4 g/kilogram/day for 5 days. The patient showed further improvement and at three months was normal. She remains well two years on. Informed consent was obtained from this patient for reporting her case.

3. Discussion

The clinical triad of ophthalmoplegia, ataxia and areflexia is in keeping with the Miller Fisher Syndrome discovered in 1956 [1]. As the years progressed, new cases were reported and anti-ganglioside antibodies were recognized as a possible pathophysiologic process underlying the disease mechanism. Therapeutic measures targeted at this pathway proved to be successful in management.

The patient had a history of a recent viral infection and subsequently developed ophthalmoplegia, ataxia and areflexia. The clinical symptoms developed within days and improved with treatment highlighting the pathogenesis of molecular mimicry known to this syndrome and antiganglioside antibodies attack-

ing extraocular nerves and Schwann cells. In Miller Fisher Syndrome, patients initially have diplopia and/or limb and gait ataxia [2]. The full clinical picture of ataxia, areflexia and ophthalmoplegia usually occurs within 5 to 10 days [2]. The Miller Fisher Syndrome is a diagnosis made on clinical grounds. The detection of anti-ganglioside antibodies in serum, CSF for elevated protein, EMG, and MRI-brain aided in reinforcing the diagnosis and excluding others. The patient presented developed similar symptoms over a period of 14 days consistent with the presentation and chronology of Miller Fisher syndrome. She also had a mild elevation of CSF protein with EMG findings supporting our diagnosis.

Antibodies to GQ1b bind to human peripheral nerves; predominantly oculomotor nerves and exhibits the a-latrotoxin-like effects [3]. This involves complement activation targeting nerve terminal architecture and Schwann cells [4] [5] [6] [7]. GQ1b gangliosides can be found in the oculomotor, trochlear, and abducens nerves [8]. The development of complex ophthalmoplegia can be explained by this as antibodies binding to myelin provoke an immune response causing demyelination. Antibodies to GQ1b are most likely induced during the infection preceding the onset of neurological symptoms by the mechanism of molecular mimicry [9].

Intravenous immunoglobulin preparations counteract these effects [10]. The immunomodulatory effects of intravenous immunoglobulin target several components of the immune system including B-cells, T-cells, macrophages, complement, cytokines and cellular adhesion molecules. Different stimuli activate B cells and they differentiate into plasma cells. Soluble immunoglobulins are produced by plasma cells against autoantigens [11]. These are responsible for the majority of clinical features in antibody mediated autoimmune diseases. The formation of immune complexes activate the classical complement cascade resulting in the production of membrane attack complexes (MAC) which induce the organ specific tissue damage seen in Miller Fisher Syndrome. The anti-inflammatory activity of intravenous immunoglobulin G is mediated by its ability to prevent the formation of MAC and subsequent tissue destruction. Inhibition of macrophage function reduces phagocytosis of antigen-presenting cells and antibody-mediated cellular cytotoxicity, thus inhibiting macrophage-mediated demyelination. Intravenous immunoglobulin also reduces the production of interleukin-2 and interferon-γ (gamma) by T-cells preventing the development of disease. These mechanisms of intravenous immunoglobulin G modulate the disease process seen in Miller Fisher Syndrome.

Miller Fisher Syndrome usually follows a benign course leading to complete remission without residual deficits [1] [2]. Relapses of Miller Fisher Syndrome are rare, but may occur with disease-free intervals [2]. Supportive treatment usually is sufficient in patients with mild disease. Intravenous immunoglobulin or plasma exchange is effective in treating patients with severe Miller Fisher Syndrome [10].

This patient presenting with ophthalmoplegia, ataxia and areflexia prompts the consideration of a demyelinating neuropathy. Although, Guillain Barre Syn-

drome has an areflexic component and a pathophysiologic emphasis on molecular mimicry as one of the underlying mechanisms responsible for disease manifestation, our patient did not fully fit this subset of immune mediated neuropathies. The added clinical findings of complex ophthalmoplegia and ataxia further reinforced the diagnosis of the Miller Fisher variant.

The learning points in this case include: the prompt recognition of clinical findings and consideration of differentials, establishing an early diagnosis in order to initiate treatment and pursuing the relevant investigations.

The other differentials that can be considered in this case are other autoimmune and non autoimmune causes. Autoimmune differentials include: sub-acute ophthalmoplegia, sub-acute ataxia, Guillain Barre Syndrome with ophthalmoplegia, pharyngeal cervical brachial variant and Bickerstaff brainstem encephalitis. Non autoimmune differentials include: brainstem lesions, neuromuscular transmission disorders, meningitis carcinomatosa and lymphomatosa, metabolic disorders, infections (Lyme's neurosyphillis, botulism), intoxications and nutritional deficiency (thiamine).

A complex eye movement disorder, ataxia and areflexia in a 35 year old female without known medical conditions should immediately lead to a detailed exploration of the prodrome and evolution of symptoms. The acquisition of the diagnosis of Miller Fisher Syndrome in this patient was based primarily on history and clinical findings. Cerebrospinal fluid analysis revealed a mildly elevated protein. Electrodiagnostic studies confirmed a demyelinating neuropathy and the presence of anti-GQ1b Ig G antibodies further reinforced a post infectious immune mediated syndrome. Treatment was immediately started with subsequent improvement of symptoms. Although after six weeks this patient had an ataxic gait, she responded to another course of intravenous immunoglobulin and remained symptom free. This highlights the underlying pathogenesis of Miller Fisher Syndrome and the course of disease with plasmapheresis or immunoglobulin administration.

Anti GQ1b antibodies is the hallmark of Miller Fisher syndrome. These antibodies are responsible for the extraocular manifestations, ataxia and areflexia seen in this patient. Management was successful with courses of intravenous immunoglobulin G.

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Echocardiographic and Clinical Evaluation of Rheumatic Mitral Stenosis in Younger and Elderly Patients

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Abstract

Background: Rheumatic heart disease (RHD) is common form of heart disease among population, especially in developing countries like India. Mitral stenosis (MS) is majorly caused by rheumatic heart disease with mitral commissural adhesion, fibrosis and calcification of the chordae tendineae. The aim of present study was clinical and echocardiographic evaluation for mitral stenosis in RHD patients with different age group. **Methods:** This was a retrospective, nonrandomized, and single-centre study in which 203 consecutive patients presented rheumatic mitral stenosis. All the patients were divided into different age group viz. <40 years, 40 to 65 years and >65 years. Cardiovascular examination and echocardiography were done in each patient. Mitral valve area (MVA), mitral valve gradient (MVG) and left atrial (LA) diameter were assessed by echocardiography. Mitral valve score was recorded to analyse the degenerative changes in mitral valve structure. **Results:** A total of 203 patients (133 females) were enrolled and divided into three age groups. Patients with age above 65 years were considered as elderly and those patients with age below 40 years were considered as younger. Echocardiographic assessment showed mean 4.7 and 4.9 cm LA diameter, 0.92 and 0.86 cm^2 MVA and 11.2 and 9.7 mm Hg MVG in younger and elderly patients respectively. Total mitral valve score has shown significant ($p < 0.001$) difference between younger and elder patients. Moreover, calcification and subvalvular thickening score with >2 had shown significant difference ($p < 0.001$) between younger and elderly patients. **Conclusion:** Present study provides unique contemporary data on characteristics and management of patients with rheumatic mitral stenosis. Majority of elderly patients are unsuitable for percutaneous commissurotomy due to degenerative changes in mitral valve structure.

Keywords

Percutaneous Commissurotomy, Rheumatic Heart Disease, Rheumatic Mitral Stenosis

1. Introduction

Mitral stenosis (MS) causes an obstruction to blood flow from the left atrium to left ventricle. As a result, there is an increase in pressure within the left atrium, pulmonary vasculature, and right side of the heart, while the left ventricle is unaffected in isolated MS. Nearly all cases of MS are caused by rheumatic heart disease with mitral commissural adhesion; thickened, immobile mitral valve leaflets; and fibrosis, thickening, shortening, fusion, and calcification of the chordae tendineae. Infrequent causes of MS include mitral annular calcification and congenital mitral stenosis [1]. MS is highly prevalent in developing countries because of its association with the prevalence of rheumatic fever but is increasingly being identified in an unusual form in developed countries [2].

Two-thirds of the world's population live in developing countries with a high prevalence of rheumatic fever or rheumatic heart disease (RHD), resulting in a large population with mitral stenosis. In a survey of rheumatic fever in India [2], the mean age of presentation was 15 years, and two-thirds of the participants had signs of mitral stenosis, of whom half had limiting symptoms. Up to 30 million school children and young adults have chronic RHD worldwide, and nearly a third of these also have mitral stenosis [3].

Echocardiography is used to diagnose and judge stage of disease, assess mitral regurgitation, exclude that mimic mitral stenosis, and provide information about suitability for percutaneous balloon valvuloplasty (PBV). Both valve area and gradient can be accurately measured, but several measurements with more than one method are often needed to accurately estimate haemodynamics of the mitral valve. The most reliable method to calculate valve area is planimetry with 2D echocardiography cross-section images [4].

Even though the prevalence of mitral stenosis is high in India, the age-specific clinical and anatomical characteristics of the disease are not well studied among Indian patients. The present study was therefore undertaken with clinical and echocardiographic evaluation for Mitral Stenosis in RHD patients who attending the cardiology services at Pariyaram Medical College, Kannur, Kerala.

2. Methods

2.1. Study Design and Patients Population

A total of 203 consecutive patients presenting rheumatic mitral stenosis at the department of cardiology, Pariyaram Medical College, Kannur, Kerala from January 2012 to May 2014 were included in the present study. All the patients were divided into different age group. However, patients with grade > 2 mitral regurgitation, more than mild lesion of the other valves and history of previous surgical commissurotomy either percutaneous or surgical were excluded from this study.

A record of physical findings was made and cardiovascular examination was done in each case. Echocardiography was carried out in all cases using a Philips, IE 33 Doppler Echocardiography system. Mitral valve area was assessed by 2D

planimetry and pressure half time method [5]. To analyse the effect of mitral valve structure due to degenerative changes, we scored the echocardiographic study of each patient for: (a) leaflet mobility, (b) leaflet thickening, (c) subvalvar thickening, and (d) calcification. Table 1 shows the scoring system [6]. This study was approved by the institutional review board (IRB) and all patients signed the written informed consent.

2.2. Statistical Analysis

Patient baseline characteristics were presented as frequency and percentages. Differences between two point estimates were determined to be statistically significant at the 0.05 level using two-sided significance tests (z-tests).

3. Results

3.1. Baseline Demographic Characteristics

A total of 203 patients were divided into three age groups viz. <40 years (68 patients), 40 to 65 years (78 patients) and >65 years (57 patients). The mean age was 52 years (17 to 90 years). Patients with age above 65 years were considered

Table 1. Scoring of mitral valve characteristics from the echocardiographic examination [6].

Variable (Scores)	
Leaflet mobility	
1	Highly mobile
2	Reduced mobility
3	Basal leaflet motion only
4	Minimal motion
Valve thickening	
1	Near normal (4 - 5 mm)
2	Thickened tips
3	Entire leaflet thickened (5 - 8 mm)
4	Marked leaflet thickening (>8 - 10 mm)
Calcification	
1	Single area of brightness
2	Scattered areas at leaflet margins
3	Brightness extends to mid leaflets
4	Extensive leaflet brightness
Subvalvular thickening	
1	Minimal chordal thickening
2	Chordal thickening up to 1/3
3	Distal third of chordae thickening
4	Extensive thickening to pap muscle

as elderly and those patients with age below 40 years were considered as younger.

The past history of acute pulmonary oedema, rheumatic fever and atrial fibrillation were present in 19 (36%), 11 (20%) and 36 (64%) for elder patients group while youngest group present with acute pulmonary oedema 4 (6%), rheumatic fever 25 (37%) and atrial fibrillation 6 (9%) respectively. Cerebrovascular accident (CVA) due to infraction was present in 14 (25%) of elderly compared to 2 (3%) of younger patients (Table 2).

3.2. Echocardiographic Examination

Assessment of echocardiography showed mean left atrial (LA) diameter of 4.7 cm, mitral valve area (MVA) of 0.92 cm^2 and mitral valve gradient (MVG) of 11.2 mm of Hg in younger patients, while mean LA diameter (4.9 cm), MVA (0.86 cm^2) and MVG (9.7 mm Hg) were present in elderly patients (Table 3).

Table 2. Baseline characteristics of three age groups of patients with rheumatic mitral stenosis.

	Age group (years)			
Parameters	<40	40 - 65	>65	*p* Value (<40 Vs > 65)
Number of patients	68	52	34	-
Females	47 (70%)	52 (68%)	34 (61%)	NS
Means NYHA Class	II	II	II	NS
	History			
Paroxysmal nocturnal dyspnea	18 (27%)	22 (29%)	22 (39%)	NS
Acute pulmonary oedema	4 (6%)	11 (14%)	19 (36%)	< 0.001
Rheumatic fever	25 (37%)	23 (70%)	11 (20%)	< 0.05
Cerebral vascular accident	2 (3%)	9 (12%)	14 (25%)	< 0.001
Atrial fibrillation	6 (9%)	23 (30%)	36 (64%)	< 0.001
Clinical features of pulmonary arterial hypertension	44 (66%)	32 (42%)	24 (43%)	< 0.01
Signs of pliable valve	66 (99%)	70 (91%)	39 (70%)	< 0.001

Values are expressed as n (%). NYHA, New York Heart Association; Significance at $p < 0.05$ calculated using a z-test comparing <40 years (younger) with >65 years (Elderly) patients; NS: Non-significant.

Table 3. Comparison of left atrial (LA) size, mitral valve area (MVA) and mitral valve gradient (MVG) of three age groups of patients with rheumatic mitral stenosis.

	Age group (years)		
Parameters	**<40**	**40 - 65**	**<65**
LA, mean (cm)	4.7	4.5	4.9
MVA, mean (cm^2)	0.92	0.9	0.86
MGV, means (mm Hg)	11.2	10.4	9.7

3.3. Mitral Valve Score

According to classification of mitral valve score as depicted in Table 1, the score of less than 8 was present in 88%, 54% and 23% of younger (<40 years), 40 to 65 year old and elder (>65 years) patients. However, 23% of elder patients had mitral valve score greater than 11 and only 2% patients had mitral valve score greater than 11 (Figure 1).

Higher calcification and subvalvular score (>2) was present in 68% and 61% in elderly patients respectively. Though, only 3% and 13% patients with younger population present with higher calcification and subvalvular thickening, respectively (Figure 2).

4. Discussion

Mitral valve disease is a common cause of morbidity and mortality in patient over age of 65. Physical findings and natural history of rheumatic mitral stenosis may differ in older and younger patients. In addition, symptoms of mitral stenosis may be masked or exacerbated by coexistent coronary artery disease, pulmonary disease, hypertension, and other systemic disorders that commonly occur in older adults [7]. According to previous published reports for the treatment of mitral stenosis, the mean age of the patients ranged from 15 to 56 years. One third of the patients who undergo percutaneous mitral valvotomy are >65 years old [8] [9]. In the present single center study that excluded the patients who had

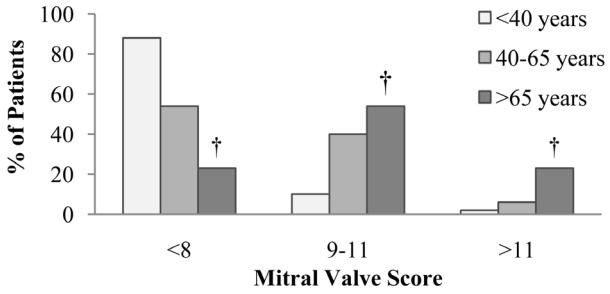

Figure 1. Comparison of mitral valve score (<8, between 9 to 11 and >11) of three age groups of patients with rheumatic mitral stenosis. †The $P < 0.001$ calculated using a z-test comparing <40 years (younger) with >65 years (Elderly) patients.

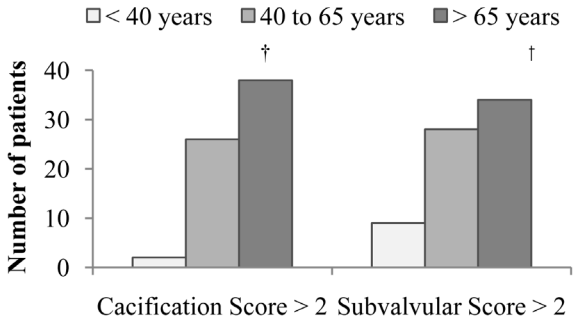

Figure 2. Calcification score and subvascular score having >2 of three age groups of patients with rheumatic mitral stenosis. †The P < 0.001 calculated using a z-test comparing <40 years (younger) with >65 years (Elderly) patients.

undergone surgical or percutaneous commissurotomy, 28% were above the age of 65 years, the oldest being 90 years of age. Only two patients (3%) were below 18 years. Two thirds of patients were females. Mean duration of dominant symptom of dyspnoea on exertion was 4.9 years that is comparable to younger patients which indicates that the disease may remain latent for many decades and may be participated by arrhythmias like atrial fibrillation which is significantly higher in elderly patients. Incidence of acute pulmonary edema was significantly higher in elderly patients (36%) than younger group (6%). Difference could be due to multiple factors like higher incidence of atrial fibrillation, lower atrial compliance, presence of diastolic dysfunction and other co morbid conditions like systemic arterial hypertension or coronary artery disease. This is contrary to earlier observations that acute pulmonary oedema occurs in the early stages of the disease in the younger patients. Average age of patients with acute pulmonary oedema in Wood's series was 32 years [10].

History of rheumatic fever is present in 60% of cases [10]. In our study 37% of younger patients gave history of rheumatic fever where as only 20% of elderly group could remember about the occurrence of rheumatic fever in childhood. Incidence of cerebrovascular accident was higher among elderly group than younger (25% vs 3%) probably due to higher incidence of atrial fibrillation. Trial fibrillation is the most common complication (40%) of mitral stenosis [10]. Aging is reported as an independent risk factor for the genesis of atrial fibrillation in mitral stenosis [11]. Moreover, Previous study showed patients who developed AF were older and had higher mitral echo score but equal mitral valve area and left atrial size [12]. According to our study, AF was significantly more common in elderly group (64% Vs 9%, $P =< 0.001$). Tandon et al. (2010) found more severe pulmonary vascular changes in younger patient [13]. These results have support to Sinha et al. (1997) findings that mean pulmonary arterial pressure and pulmonary vascular resistance are greater in juvenile patients with mitral stenosis when compared with adults [14]. In our study also clinical evidences of pulmonary arterial hypertension, electrocardiographic evidence of right ventricular hypertrophy, radiology evidence of main pulmonary artery dilatation; electrocardiographic feature of right ventricular dilatation (RVIDd > 2.6 cm) and pulmonary arterial systolic of more than >50 mmHg were significantly more common among younger age group.

On echocardiographic evaluation, elderly patients had left atrial size of 4.9 cm while it was 4.7 cm in the younger group. Mean mitral value area was 0.86 cm^2 in the elderly and 0.92 cm^2 in younger group. In addition, mean mitral valve gradient was 9.7 mm Hg in elderly and 11.2 mm Hg in younger patients. Despite similarity in mitral valve area and mitral valve gradient, total mitral valve score of <8 was statistically more common among younger group and >11 was statistically more common among elderly group (**Figure 1**). Fawzy et al. has shown that lower in mitral echo score, mitral valve area and higher Doppler mitral valve gradient were observed in younger (<20 years) when compared to adults (>20 years) [15]. Older patients had more severe degree of mitral stenosis, with

higher mitral valve degenerative changes. After balloon dilatation the younger patients achieved a greater increase in valve area. Moreover, procedural success was higher in the younger group with a greater increase in mitral valve area but complications were similar in both groups. In our study among elderly group, approximately 80% of patients were not suitable for closed mitral valvotomy or percutaneous commissurotomy. Complications of balloon valvotomy were more common in the older patients [16].

5. Conclusion

In older patients there is a greater tendency for valve degenerative change in addition to commissural fusion, and such patients often have co-morbidities. Majority of younger patients (88%) have Wilkin's score of <8, while most of elderly patients (77%) have score more than 9 despite having similar mean mitral valve area and mean mitral gradient. Thus, in older patients, improvement may be made by palliative treatment for those unsuitable for surgery.

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Food Allergy Mimicking Pylorus Hypertrophy

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Abstract

Food allergy (FA) is a disease with increasing prevalence and a wide spectrum of clinical manifestations. These include the eosinophilic disorders, which can involve any segment of the gastrointestinal tract (GIT), including the stomach. In this context, three patients with a confirmed diagnosis of food allergy, who were initially diagnosed with pyloric hypertrophy, are presented. All cases showed an adequate response to nutritional management. It is essential to consider food allergy, such as eosinophilic gastroenteritis, as part of the differential diagnosis of gastric outlet obstruction in those patients who present vomiting secondary to pyloric hypertrophy.

Keywords

Food Hypersensitivity, Hypertrophic Pyloric Stenosis, Eosinophilic Gastroenteritis

1. Introduction

Food allergy (FA) is being seen with increasing prevalence and wide spectrum of manifestations. Within its spectrum, manifestations can appear in the respiratory or gastrointestinal tract and the skin. The immunological mechanisms that develop the disease can be immunoglobulin E mediated, cell mediated or both.

Eosinophilic disorders, that are part of this spectrum, cell mediated, of disease presentation, sometimes become a challenge in the diagnosis. Three patients with a confirmed diagnosis of food allergy who were initially misdiagnosed as pyloric hypertrophy are presented. All cases resolved with adequate nutritional management.

2. Case Reports

Case No. 1.

Male infant 2 months and 17 days old with a history of prematurity due to

multiple gestation, cesarean delivery, intrauterine growth restriction (IUGR), neonatal pneumonia, and bronchopulmonary dysplasia. From the first month of life, the patient presented postprandial vomiting. Hypertrophic pyloric stenosis (HPS) was diagnosed through ultrasound. At 2 months old, he underwent pyloromyotomy. After surgery, the frequency of vomiting decreased, without completely disappearing. In addition, he presented irritability for more than three hours daily, food refusal, frequent hiccups, dysphagia, and Sandifer position, symptoms that do not respond to treatment with ranitidine and *Lactobacillus reuteri*. Given the persistence of vomiting and other symptoms, the patient was submitted for evaluation by pediatric gastroenterology. As a background, allergic rhinitis was found in both parents. From birth he received breast-feeding, supplemented with infant formula based on cow's milk protein (CMP); up to the date of the examination, 3 different formulas were tried. The physical examination was within normal limits, and anthropometry for the corrected age showed chronic malnutrition. Because of these symptoms, malnutrition, the type of food received, and a history of allergies in both parents, the diagnosis of FA was considered, possibly eosinophilic esophagitis and/or the enteropathy type. He was given an L-amino acid formula (AAF), and CMP restrictive diet was prescribed for the mother. Despite this, symptoms persisted, so breastfeeding was stopped, and only AAF continued. After this treatment, the vomiting stopped and he gained weight, so the diagnosis of food allergy was confirmed. The initial ultrasound of the pylorus was reviewed, and a pyloric wall thickness of 4mm with a channel length of 17 mm was observed. However, during feeding, passage of gastric contents through the pylorus was seen.

Case No. 2.

23-day-old female, admitted to the neonatal intensive care unit with uncontrollable vomiting and poor weight gain. Laboratory tests were taken in order to rule out an infectious process. Abdominal radiography was requested, on suspicion of enterocolitis, which was discarded. Abdominal ultrasound was performed, resulting in a diagnosis of HPS. The pediatric surgeon considered performing pyloromyotomy. The patient was assessed by the pediatric gastroenterologist, finding that bowel movements exhibited normal characteristics. Cell blood count (CBC) showed peripheral eosinophilia of 6%, and atopy was described in both parents. On physical examination, the pyloric olive was not felt. Because of suspected FA, prior to surgery it was decided to feed the patient with extensively hydrolyzed formula (EHF), with favorable response. There was cessation of vomiting and progressive weight gain, and therefore it was decided to postpone the surgery. The radiologist again reviewed the ultrasound. The diameters were recalculated, finding a thickening of the mucosa rather than the muscle layer (3 mm thick and 17 mm in length in the pyloric channel). After 5 days of nutritional management with EHF, abdominal ultrasound was performed, and result normal (pyloric channel length 17 mm × 1.5 mm thick in the antrum).

Case No 3.

Male patient, 4 months old, since 20 days old presented with 3 hours postprandial non bilious vomiting, the initial diagnosis was gastroesophageal reflux. During the first month of life he was hospitalized because of persistent vomiting despite pharmacological management, with dehydration. No visible peristalsis nor palpable mass was evident on physical examination. Pylorus ultrasound, which reported 3.3 mm wall thickness and pylorus of 15.6 mm in length, was performed. Given the persistence of emesis, he underwent pyloromyotomy. During the postoperative period, he was fed with lactose-free formula and then was discharged. On the second day after surgery, the patient presented diarrhea, with 12 mucoid stools per day, persistent vomiting, regurgitation, and dysphagia. The formula was changed to EHF, without improvement. Therefore, he was remitted for pediatric gastroenterology consultation. Medical history of importance: cesarean delivery at term with normal weight and height at birth, breastfeeding for a month and parent's urticaria. On physical examination, eczema of the cheeks was found, anthropometry was normal, but at risk of stunting. Suspecting FA, the formula was changed to AAF. Three weeks after the change, the eczema and vomiting disappeared, the frequency of stools decreased, and there was improvement in his length.

3. Discussion

Vomiting is one of the most common symptoms in the first few months of life. The vast majority is of benign origin and self-limited, as is the physiological reflux. However, in newborns and in the first months of life, nausea and recurrent non-bilious vomiting require additional study to rule out malformations of the gastrointestinal tract and gastric outlet obstruction syndrome. In pediatrics, the most common cause of this obstruction syndrome is hypertrophic pyloric stenosis (HPS). The clinical history and a physical examination are essential for diagnosis. However, in order to define it, radiological images are usually needed [1]. Other causes responsible for the symptoms have been described, including antral membrane, gastric volvulus, duplication cysts, polyps, intestinal malrotation, and neoplasms, though these are less frequent [1]. There are also reports in the literature of gastric outlet obstruction secondary to eosinophilic gastroenteritis (EG), consistent with our subject of interest.

HPS is the most common childhood surgical pathology, manifested by non-bilious vomiting. It was described by Hirschsprung in 1888. The first successful surgical correction was performed by Ramstedt in 1912 [2]. The incidence in infants is variable, reported in 2-5:1000 live births in the United States [1]. In Africa and Asia, the incidence is lower, approximately 1:1000 live births [3]. No data exist on the incidence in Colombia. The incidence in older children is unknown. Usually it occurs in infants aged 2-12 weeks with postprandial uncontrollable vomiting. It is characterized by hypertrophy of the circular smooth muscle layer of the pylorus, which causes a thickening and elongation of the pyloric canal, findings that should be corroborated with ultrasound. The following also appear: gastric chamber dilation and an increased gastric peristalsis as com-

pensation mechanisms [2]. These changes may be evident on physical examination through palpation of the "pyloric olive" and visible peristalsis, although none of these findings were present in our cases. The etiology of HPS is unclear. However, the following have been described as triggers: abnormalities in the hormonal control, intrinsic abnormalities of muscle fibers, the cells of Cajal and nerve fibers, infections, and increased insulin-like growth factors, as well as genetic predisposition. To date none of the theories fully explains the development of the disease [2] [4]. On the other hand, Krohg and collaborators listed a number of risk factors for the development of HPS, including: male gender, the use of macrolides, and bottle feeding, without having been able to clarify whether the cause is infant formula per se or technical supply [5] [6]. In addition to the vomiting, the disease may be accompanied by hypochloremic alkalosis and indirect hyperbilirubinemia [7]. These biochemical abnormalities, which were not documented in the cases submitted (see **Table 1**), are useful in the diagnosis and therefore are included in the algorithm (**Figure 1**).

Ultrasound imaging is the method most widely used for the diagnosis of HPS, replacing studies with contrast media used initially. Thickness of the musculature of the antrum ≥4 mm, accompanied by an elongation of the pyloric chan-

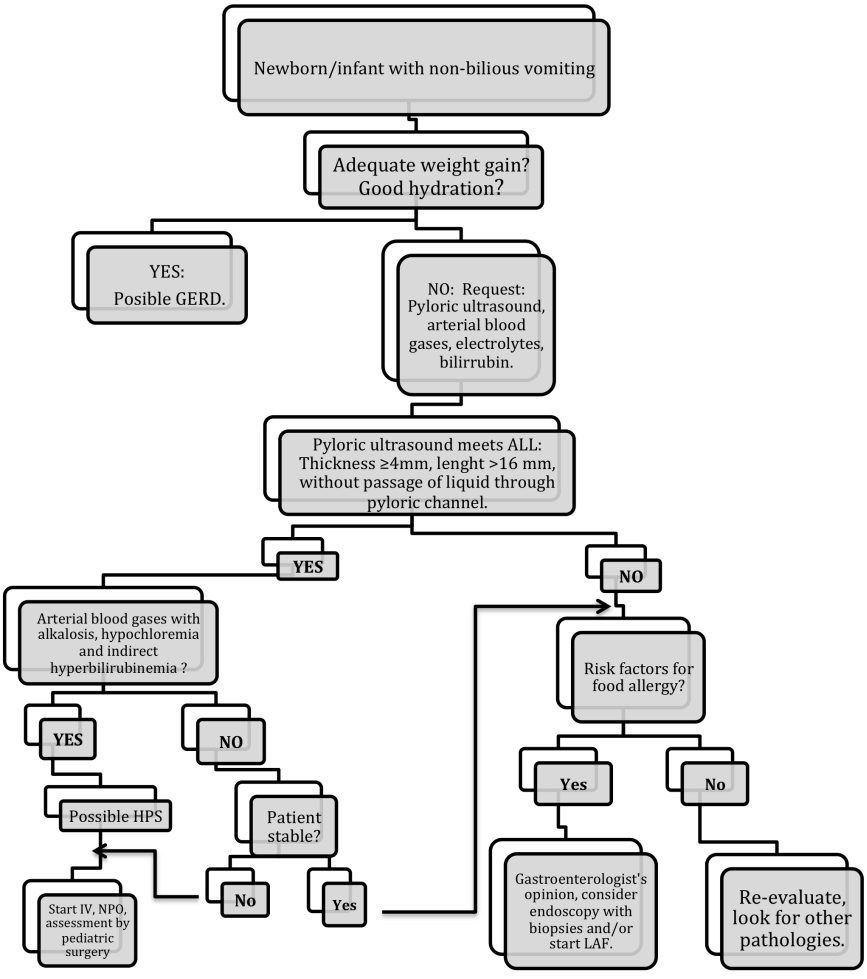

Figure 1. Diagnostic algorithm for neonates/infants with vomiting.

Table 1. Laboratory values in patients submitted (Source: Gastronutriped).

Case	Age	Pyloric Thickness (mm)	Pyloric channel length (mm)	Passage of iquid through pyloric channel	Seric chloride (meq/l)	Bilirrubin (me/dl)	Peripheral eosinophilia (%)	PH/HCO_3
1	2 month	4	17	Yes	Normal	NR	11	NR
2	23 days	3	17	No	Normal	Normal	6	NR
3	1 month	3.3	15.6	No	Normal	TB: 10.12 IB: 9.53	12	7.36/24.2

NR: No Report.

nel >16 mm are the findings needed for the diagnosis. Based on these parameters, the second and the third patient did not meet the diagnostic criteria for HPS.

A thickness of 2 to 3 mm is nonspecific; a value less than 2 mm is considered normal. Pyloric spasms and distension of the gastric antrum with liquid can give the false impression of muscle thickening [8]. For borderline measurements, pyloric channel relaxation after administration of liquid to the stomach excludes the diagnosis of HPS [2]. Although the first case met the ultrasound diagnostic criteria, abnormal measurements could have been due to a "fake" thickening by edema of the gastrointestinal mucosa due to FA; other diagnoses were excluded on the evidence of the passage of gastric contents through the pylorus.

Pyloromyotomy is the surgical treatment of choice for HPS, preferably using the laparoscopic technique, because of the shorter recovery time and lower complication rate. Clinical improvement of HPS has been described with oral administration of atropine; however, treatment failure of 25% and the time it takes for resolution of symptoms make this treatment not routinely recommended [2].

Kaijser first described EG in 1937 [9]. It can occur at any age, with male predominance, as happens with HPS [10]. It is characterized by a diffuse infiltration of eosinophils, which can affect different layers of the GIT, from the esophagus to the anus [11]. There is no consensus for diagnosis; however, Talley proposed three criteria: the presence of gastrointestinal symptoms, biopsies showing eosinophil infiltration into one or more areas of the GIT, and exclusion of parasitic infections and/or extraintestinal disease [12]. Although peripheral eosinophilia is not a diagnostic criterion, its presence increases suspicion [13], as happened in case N.2. EG consists of three histologic types depending on the layer involved. The most common compromise is in the mucosa, in 60% of cases, followed by the muscle (30%) and to a lesser extent (10%) the involvement of the subserosa [14]. The predominant clinical expression is secondary to the infiltration of eosinophils in the mucosa, which causes malabsorption and failure to thrive, the latter observed in cases 1 and 3. Also, the involvement of the muscular layer can predispose the patient to obstructive symptoms. If this involvement is antral, it can be confused with HPS [11], a fact which we assume happened in the three

patients described. Already in 2007, Liacouras suggested that EG should be suspected in an infant with vomiting, dehydration, electrolyte imbalance, and thickening of the gastric outlet, if there are also symptoms of atopy [11]. This is very similar to that described in our three patients and is consistent with the favorable response to nutritional management with AAF. Also, there have been reports of older children and adults with similar symptoms, with suspected HPS, where the symptoms resolved with medical treatment [10] [15]. Since eosinophil infiltration into tissues is segmental, histologic confirmation is difficult, and therefore multiple biopsies should be taken [9]. In EG, thickened mucosa and submucosa can coexist, in contrast to HPS, where the condition is manifested exclusively in the muscle layer. To be reliable, the ultrasound should be performed with a high-frequency linear transductor (7-MHz) [9]. The ultrasound findings help to clarify the diagnosis; however, they are operator dependent and require a high index of suspicion and expertise to avoid confusion, as in case N.2. If in doubt, the opinion of the pediatric gastroenterologist is important, in order to resolve the diagnosis by performing an upper endoscopy with segmental biopsies.

Medical treatment is the mainstay for the management of GE. As part of this treatment, EHF, AAF, and/or allergen elimination diets may be used, which have been found to show clinical and histological improvement. However, there is no consensus with respect to this recommendation [13]. Also, the use of systemic steroids has demonstrated remission of symptoms and normalization of endoscopic, ultrasonographic, and histological findings [11]. In our three patients, symptoms improved with nutritional intervention, two with AAF and one with EHF. Some medications, such as cromolyn sodium, montelukast, anti-IgE, and anti interleukin 5, have some immunomodulatory effect; however, there is insufficient evidence to suggest their routine use [10] [11] [14]. Surgical treatment is reserved for patients with symptoms of obstruction that do not respond to medical treatment [14] [16]. In general, the prognosis of the disease is favorable, as evidenced in the follow-up of the three patients, who continue to be symptom free and with adequate growth and development.

4. Conclusion

HPS is a condition to be considered in the diagnosis of infants with recurrent emesis and symptoms suggestive of gastric outlet obstruction. However, food allergy (FA) should be included as a differential diagnosis, particularly when there are risk factors for allergic sensitization such as c-section, lack of or short duration of breastfeeding, early use of antibiotics, and first-degree relatives with atopy, as we described in the cases presented. While pyloric ultrasound is the most widely used diagnostic method for suspected HPS, it should be remembered that ultrasound findings may be present in both conditions. When the diagnosis of HPS is doubtful, performing a medical therapy trial and/or endoscopic biopsies should be considered as part of the differential diagnosis algorithm (see **Figure 1**).

Conflict-of-Interest Statement

Authors declare that there are no conflicts of interest to disclose.

Authors declare that the parents/guardians of the patients were informed and agreed to the publication of these cases for strictly academic purposes**.**

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The Effect of Pomegranate Paste on Neonatal Jaundice Incidence: A Clinical Trial in Women during Pregnancy

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Abstract

Purpose: Some topics such as women's life style and nutrition and using some special medicines during pregnancy have been discussed and demonstrated as effective factors on infant' health. Based on recommendations in Iranian traditional medicine, we aimed to evaluate the efficacy of pomegranate paste consumed by women during their pregnancy on the neonatal jaundice incidence. **Methods:** In this single-blinded controlled clinical trial, 80 healthy pregnant women were randomly divided into 2 groups, as treatment and control. The treatment group members added pomegranate paste to their daily diet from the 34th week of the pregnancy to birth, as administered. The levels of neonates' bilirubin were checked in the 5th day of the delivery. **Results:** Both the need of phototherapy and the mean level of neonates' bilirubin in the group fed with pomegranate paste were significantly lesser compared to control group. The number of neonates who were undergone phototherapy in the pomegranate paste receiving group was significantly lesser than that in the control group (P value = 0.029). By measuring the total bilirubin, statically significant difference between the treatment group and the control group was seen (P value = 0.021). **Conclusion:** The results of this study suggest the possible effect of adding pomegranate paste to pregnant women's diet on the incidence of neonatal jaundice.

Keywords

Pomegranate, Hyperbilirubinemia, Neonatal Jaundice, Pregnancy, Iranian Traditional Medicine

1. Introduction

Neonatal jaundice is a common complication in newborns seen in 60% of term and 80% of preterm, during the first week of life [1]. It is mostly benign, however, in some cases may turn into catastrophe and needs to be taken seriously. High level of bilirubin for prolonged periods of time could result in permanent brain damage [2].

Although phototherapy is suggested as the first-line treatment of hyperbilirubinemia in neonates, it may put the infant at the risk of important complications such as retinal injury, loose stools, erythematous macular rash, purpuric rash, overheating, dehydration, hypothermia, and a benign condition called bronze baby syndrome [1] [3].

Nowadays, effective prevention of unfavorable and dangerous jaundice requires ongoing vigilance and a practical system-based approach in order to distinguish infants with benign neonatal jaundice from those whose course may be less predictable and potentially harmful [3]. Majority of relevant studies have directed their attention on prevention of jaundice in infants, especially those with risk factors [3] [4].

Although some topics such as women's life style and nutrition and using some special medicines during pregnancy have been discussed and demonstrated as effective factors on infant' healthy [5], to the best of our knowledge, there is no specific, proved or practical recommendation for women during pregnancy to prevent occurrence of jaundice in their newborns.

Various medicinal herbs and traditional medicine remedies have been used for neonatal jaundice for ages globally [6] [7] [8]. Recently, herbal medicines have received a particular attention to discover and develop bilirubin-lowering agents in newborns [8] [9].

According to Iranian traditional medicine references, pomegranate (*Punica granatum* L.) and its paste possess cold temperament and improve function of liver and biliary tract [10] [11] [12]. It is worth mentioning that in folk medicine of Iran, pomegranate juice has been extracted manually by compressing the arils. Enjoying this method, the astringent constituents such as tannins (responsible for concern to use pomegranate products in pregnancy) are not allowed to enter the juice [12] [13] [14] [15].

In the light of the above mentioned points and since health hazards have not been reported in proper administration of taken routine dosages of pomegranate paste and while it is considered as safe in pregnancy [12] [14] we designed a single-blinded clinical trial to investigate the rate of occurrence of jaundice in newborns whose mothers had consumed pomegranate paste from 34th week of their pregnancy compared to control group.

2. Materials and Methods

This single-blind randomized clinical trial was carried out in Lolagar Hospital, Teheran, Iran, from February to August 2015. The performed protocol of the study was approved by the ethical committee on human research of Shahid Sa-

doughi University of medical sciences, Yazd, Iran. The clinical trial has been registered in Iranian registry of clinical trials (IRCT) database under code: IRCT2015010314760N2.

Eighty nulliparous pregnant women aged between 18 - 35 years were invited to participate in the clinical trial. Pregnant women with any underlying diseases such as diabetes, hypertension, hypothyroidism, and etcetera were excluded from the study. Written informed consent was obtained from all of the participants.

Ripe and sweet pomegranates were purchased from a local store in Kan, Tehran, Iran. The washed fruits were manually peeled and the yielded arils were compressed to extract the juice. The seeds were separated and the filtered juice was conventionally heated and stirred at 90˚C for 3 hours to achieve proper viscosity and formation the paste [12] [15] [16] [17].

The participants were assigned into two 40-member groups: 1. the pomegranate paste group (PG) in which the cases were advised to take 1 table spoon of the prepared pomegranate paste, twice a day, before meal from 34th week of the pregnancy until delivery, and 2. the control group (CG) whose members were advised to keep on their routine diet.

The participants were requested to attend our hospital on the 5th day of their childbirth to measure the total serum bilirubin concentration using a Bilitest transcutaneous bilirubin measurement device. The mothers were requested to inform us immediately in the case of witnessing visible icterus before the appointed time. The neonates whose apgar was below 8, and the neonates whose gestational age was less than 38 weeks, have been excluded.

One-way analysis of variance (ANOVA) and chi-square test were performed to analyze the collected data. P values < 0.05 were considered statically significant.

3. Results

A flow chart for the study is shown in the **Figure 1**. 40 women were allocated to the control group and 40 to the pomegranate paste group. 6 women from CG and 10 from PG were excluded prior to attention scheduled follow-up visit.

There were no statistically significant differences between the two groups with respect to baseline data such as body mass index (BMI), age of subjects, the type of delivery and the neonates' gender and weight (**Table 1**). The number of neonates whom were undergone phototherapy in the PG was significantly lesser than that in the CG (**Figure 2**. P value = 0.029). By measuring the total bilirubin, statically significant difference between the PG and the CG was seen (**Figure 3**, P value = 0.043 and **Figure 4**, P value = 0.021).

4. Discussion

In spite of the fact that many researchers have evaluated the effect of herbal remedies on occurred neonatal jaundice, to the best of our knowledge there is not any reported study in which the incidence of jaundice is evaluated in newborns

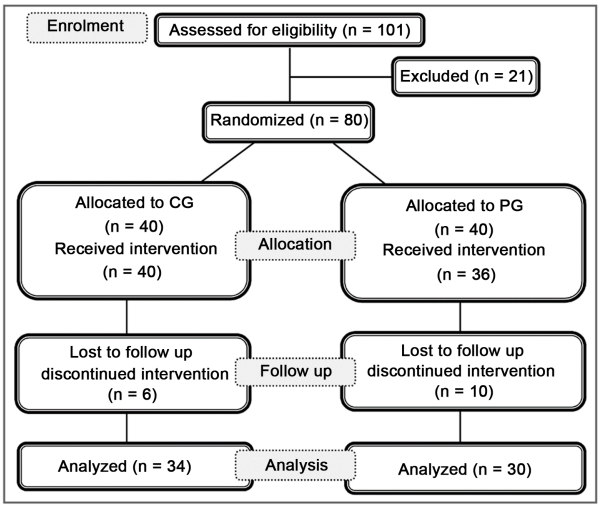

Figure 1. Flow chart of the study.

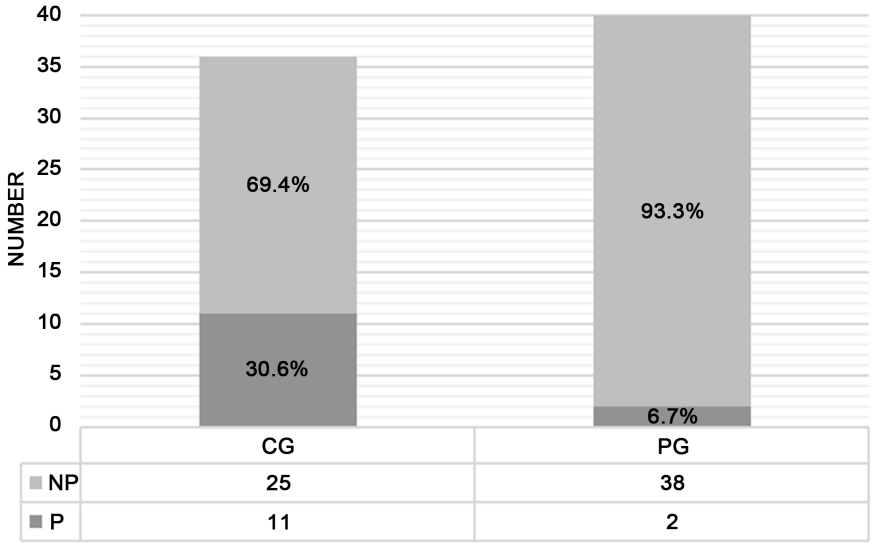

Figure 2. Comparison of the number of the newborns who needed phototherapy (P and NP stand for "performed" and "not performed", respectively. *P* value = 0.029).

Table 1. Distribution of women according to baseline variables (•Chi-square, *ANOVA).

Variables		CG	PG	*P* value
Participant's age (years)		23.3 ± 3.6	24.6 ± 4.6	0.244*
Participant's BMI (kg/m²)		22.2 ± 3.9	23.23 ± 4.8	0.216*
Participant's weight gain (kg)		16.9 ± 6.6	16.1 ± 5.8	0.433*
Type of delivery	Vaginal	17 (47.2%)	7 (23.3%)	0.098•
	Caesarian	19 (52.8%)	23 (76.7%)	
Neonates' weight (gram)		3334.7 ± 348.0	3266.6 ± 404.5	0.395*
Neonates' gender	Female	18 (50%)	16 (53.3%)	0.744•
	Male	18 (50%)	14 (46.7%)	
	Male	18 (50%)	14 (46.7%)	

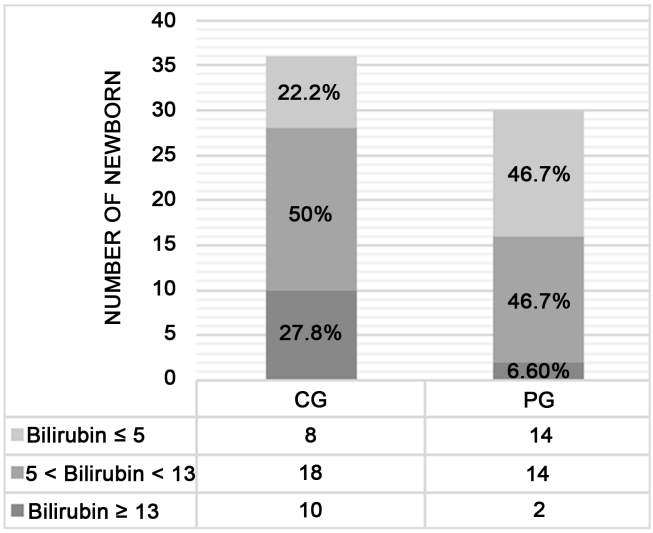

Figure 3. Comparison of the levels of bilirubin in blood samples (*P* value = 0.043).

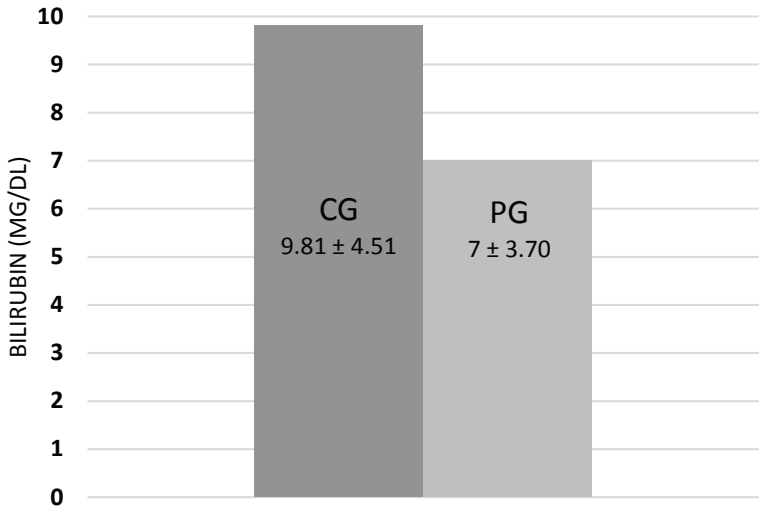

Figure 4. Comparison of the bilirubin level between groups (mean ± SD, *P* value = 0.021).

whose mothers took natural products as "prophylactic" during pregnancy. In addition, as far as we know, this is the first randomized comparative trial of the pomegranate paste in the field of jaundice, globally.

Different varieties of pomegranate—the fruit of *Punica granatum* L. belonging to the family Lythraceae-known as a nutritious fruit in Quran, have been administered in the Iranian traditional medicine to treat hepatic and biliary tract disorders such as jaundice [10] [12] [18]. It has been known and prescribed as tonic to reinforce liver and gastrointestinal tract, to treat jaundice, as hematopoietic in anemia, to treat urinary tract infection, for fatigue feeling, in depression and melancholia and many other complications [10] [12] [15] [19] [20] [21] [22] [23].

Recently, clinical trials have been in progress exploring the beneficial effects of pomegranate's various extracts. Several fields of potential clinical applications of

pomegranate have been reported in recent years, showing the importance of such natural product in skin care, dental and periodontal conditions, different types of cancer, atherosclerosis, hypertension, diabetes, depression, erectile dysfunction, male infertility, ischemic brain injury, Alzheimer's disease, obesity, inflammation, hyperlipidemia, carotid artery stenosis etcetera [19] [21] [22] [24] [25].

Some researchers and references consider pomegranate arils as safe during pregnancy [12] [14] [26]. On the other hand, the pomegranate seed's astringent polyphenols such as tannins have been reported and known unsafe during pregnancy for their emmenagogue and uterine stimulant effects [13]. This controversy may be due to the difference in the extraction method leading to different chemical composition of the final product. Iranian traditional medicine has advised to use sweet pomegranates' arils (the specialized outgrowth from the seed that completely covers that) for preparing pomegranate various products such as juice and paste and it has been highly recommended to separate the inner seed before processing [10] [12] [18] [27].

In Iranian traditional medicine, jaundice has its roots in liver's excessive warmness [10] [12] [27]. According to Iranian traditional medicine written literature, pomegranate could decrease the blood and liver warmness in pregnant women leading to decline the warmness of their fetus's liver. The decline of fetus liver warmness improves its function, and as a result, incidence of jaundice is reduced [10] [12] [27].

Our findings demonstrated the effectiveness of pomegranate paste for the first time in the incidence of jaundice in newborns whose mothers used it during pregnancy as administered.

Regarding the consumption of pomegranate paste according to the direction by the mother's perfectly, we have no choice but to trust on their own reports.

Further investigations are needed to shed more light on the involved mechanisms of action and to confirm or refute pomegranate paste clinical prophylactic effects on neonatal jaundice.

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Conflict of Interests

The authors declare that they have not any financial interests.

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Comparing EMLA Cream and Ibuprofen on Pain after Insertion of Copper Intrauterine Device

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Abstract

Background and Objective: IUD is a safe, effective, and reversible method throughout the world, particularly in areas where population growth is too much. One of the main barriers to use IUD is the fear and pain of its insertion. Therefore, it is necessary to take measures to reduce the pain, and this study was conducted to investigate the effect of EMLA cream and ibuprofen on pain during IUD insertion. **Materials and Methods**: This randomized controlled clinical trial study was conducted on 120 women who admitted to Imam Javad health center in Zahedan in 2015-2016 for insertion of IUD. Women who admitted to this center were randomly assigned into 3 groups of EMLA group (n = 40), ibuprofen (n = 40), and control or placebo (n = 40). These women have no problem to insert IUD. Demographic data and pain level were recorded in a questionnaire based on Johnson's Visual analog scale of pain at 3 stages of IUD insertion, and all IUDs were inserted by a midwife and then data were analyzed by SPSS software. **Findings**: The results of this research show that the lowest level of pain severity at three stages of insertion related to the EMLA cream ($P < 0.01$), while the maximum level of pain in the 3 groups related to Tenaculum. **Conclusion**: The results of the study showed that, compared to ibuprofen and placebo, EMLA cream is a safe method in reducing pain caused by IUD insertion in all stages of IUD insertion.

Keywords

EMLA Cream, Ibuprofen, Women-Pain Severity, IUD

1. Introduction

IUD is used as an effective, reversible, and long-term contraceptive method over the world for 30 years. It is effective for 12 - 10 years and its effect is similar to tubal ligation so that annually more than 150 million women in the world use IUD, most of whom are living in developing countries of Southeast Asia and the

Middle East, and European countries at lowest level. One of the reasons for lack of using IUD is wrong scientific information about it [1]. Scientific information indicates that the IUD is an effective method for 12 years and IUD, as a reversible procedure, does not jeopardize fertility and reproduction. IUD does not increase breast and cervical complications and female genital tract cancers. In addition, it also reduces the risk of endometrial cancer, and IUD is suggested as emergency contraception in cases that one of them has no protection [2]. One of the obstacles to use this method of contraception is the fear and the pain caused by its insertion [3]. Female genital tract mucous membranes is very sensitive to pain, and many of small procedures in this area are conducted without analgesia [4] [5] IUD, as some of the methods of diagnosis and surgery in some individuals, may be associated with high anxiety and pain, and it can make the insertion of the IUD difficult [6]. Studies have shown that about half of the people suffer moderate to severe pain during the insertion of IUD [7]. This feeling varies from low pain and discomfort to severe cramps, along with nausea and weakness [3]. As the number of nerve endings in the cervix area and internal cervical hole is more than that in the corpus of the uterus [8], the insertion of IUD can be followed by pain and discomfort through the use of Tenaculum to keep the cervix, right off the path to Tenaculum, entering Hysterometer, and the entering of IUD canola into uterus. The factors that cause increased pain during IUD insertion include being nullipara by the person, the age of more than 30 years, long time distance from the last menstruation or pregnancy and breastfeeding, and lack of natural childbirth, history of inserting IUD [9]. In the case of non-relieving of the pain, these factors increase the risk of shock and vasovagal and dangerous cardiac arrhythmia [10] [11]. In many of the clinics, ibuprofen and preparations, non-steroidal drugs, anti-inflammatory drugs, and cervical emollient drugs (misoprostol) and a topical anesthetics to alleviate the pain during the IUD insertion are used [5] [7] [10]. One a local anesthetic drugs is EMLA cream 5% that each gram of this cream contains lidocaine 25 mg and prilocaine 25 mg [12]. The analgesics application of this cream is topical on the cervix made to perform laser surgery procedures, hysteroscopy, and Hysterosalpingography [13] [14] [15]. As the insertion of IUD is a painful process and currently in the global standard method and health instructions, pain medication is prescribed to reduce the pain caused by IUD insertion, this study was conducted to compare the effect of ibuprofen and EMLA cream in reducing the pain caused by IUD insertion.

2. Materials and Methods

This clinical controlled trial study was conducted on women admitted to Imam Sajjad health center of Zahedan to insert the IUD in 2015-2016. To determine the sample size on the basis of Allen *et al.* [16] study, the number of samples was considered 32 people for each group and 40 people in each group considering the drop out possibility of the samples, using M = 3.6 and SD = 1.1 and considering $\alpha = 0.05$ and power = 90% for diagnosis of at least reduction in pain level.

According to IUD insertion instructions, the admitted women had no problem to insert the IUD. The prohibited use of IUD included pregnancy, genital infection, the risk of pelvic infections or sexually transmitted disease (in the current conditions or within the last three months), cervical or endometrial cancer, or undiagnosed genital bleeding, uterine abnormalities and fibroid tumors caused uterine cavity deformation, allergy to copper and Wilson disease [3]. Exclusion criteria included no-use of pain relief drugs in 6 hours, the lack of a history of severe stress, allergy to EMLA cream, withdrawal of the person to participate in research, and uterine depth less than 6 or 9 cm. It is worth mentioning that IUDs of 3 groups were inserted by a midwife at menstruation. People were randomly assigned in three groups in terms of receiving EMLA cream 7 minutes before insertion, receiving two ibuprofen tablets 400 mg, and 45 - 60 minutes before insertion, receiving the placebo (lubricant gel) 7 minutes before insertion. Based on previous studies, the intervention variables, which had the greatest confounding effect on the pain level such as lesions cervical of history, the history of inserting IUD, age, parity, type of childbirth, and breast-feeding in groups were homogenized. Data collection tool was researcher-made questionnaire used to record the individual information and history of midwifery and the checklist of researcher observations, and 10 cm visual analog scale (VAS). The score zero was considered as no pain, score 3 - 1 was considered as mild pain, score 6 - 4 was considered as moderate pain, and the score 9 - 7 was considered as severe pain and score 10 was considered as very severe pain. This tool was the standard scale that its validity and reliability have been proven during different studies [7] [15] [17]. To determine the validity of the midwifery questionnaire, content validity method was used. The used EMLA cream is 50 mg cream that contains 25 mg lidocaine and 25mg prilocaine manufactured by the pharmaceutical company in Sweden with production series of 003021. The used Ibuprofen tablet included 400 mg ibuprofen tablets manufactured by Aria pharmaceutical company, which two tablets were used before IUD insertion. After selecting the samples, sufficient explanations were provided about the goals and the groups for samples and their written consent was obtained. The vagina and cervix of people in the EMLA cream and lubricant gel groups were evaluated in terms of inflammation and unnatural findings and discharges after being exposed at the lithotomy position of external genitalia tract. Then, the uterine was examined by two hands and uterine size and position were determined. After 2 times of washing of the vagina and cervix with betadine, 5 g of EMLA were placed by cotton swap on cervix environment and external hole of cervix. It lasted 7 minutes to begin the anesthetic effect of cream. Then, the pain level was assessed at three stages of IUD insertion using visual analog scale. In the control or placebo group, lubricant gel was used instead of EMLA cream. Ibuprofen group subjects received 400 mg ibuprofen tablet 45 - 60 minutes prior to insertion. Data were analyzed using SPSS 20 software by using descriptive statistics and kendallk's tau-b, chi-square, and Friedman tests. In interpreting the results, p values less 0.05 were considered significant.

3. Findings

The findings of this research showed that the mean age of the women who participated in this research was 26.75 ± 6.33. To determine the correlation between the severity of pain in any of the stages and confounding variables, kendall's tau-b s test was used. This test showed significant difference between the variable of maternal education and employment and the history of inserting the IUD and type of delivery and the pain severity of Tenaculum applying ($p < 0.001$). In addition, the test showed a significant difference between education, method of delivery, the severity of pain in the stage of entering the hystrometer ($P < 0.000$). In addition, this test showed there is significant difference between the education, the history of inserting IUD, and type of delivery at the stage of IUD insertion ($p = 0.003$). Figure 1 showed the trends of pain in three groups of participants in various stages. In all stages, controls had the highest level of pain and EMLA had the lowest levels of pain.

Friedman's Non-parametric test used to measure the pain severity at three stages of insertion in the EMLA group showed that EMLA cream reduced significantly the pain from the stage of applying the Tenaculum (3.23 ± 0.78), to the stages of Hyetometer entering (2.43 ± 0.82), and the insertion of IUD (1.75 ± 0.74). In addition, Friedman's Non-parametric test used to measure the pain severity at three stages of insertion in the ibuprofen group showed that taking the ibuprofen reduced the pain from the stage of applying the Tenaculum (5.80 ± 0.82), to the stages of Hyetometer entering (4.55 ± 0.82), and the insertion of IUD (4.33 ± 0.74). In addition, Friedman's Non-parametric test used to measure the pain severity at three stages of insertion in the placebo group showed that pain severity reduced from the stage of applying the Tenaculum (6.38 ± 0.99), to the stages of Hyetometer entering (5.05 ± 0.94), and the insertion of IUD (4.75 ± 0.89) ($p < 0.001$) (Table 1).

Table 1. Friedman's Non-parametric test to measure pain severity at three stages IUD inserting.

groups	pain stage	Mean	SD	Mean rank	Chi-Square	*p*
Emla	First stage	3.23	0.78	2.39	49.24	<0.001
	Second stage	2.43	0.82	1.95		
	Third stage	1.75	0.74	1.66		
Ibuprofen	First stage	5.80	0.82	2.50	37.46	<0.001
	Second stage	4.55	0.77	1.83		
	Third stage	4.33	0.74	1.68		
Control	First stage	6.38	0.99	2.48	35.52	<0.001
	Second stage	5.05	0.94	1.84		
	Third stage	4.75	0.89	1.69		

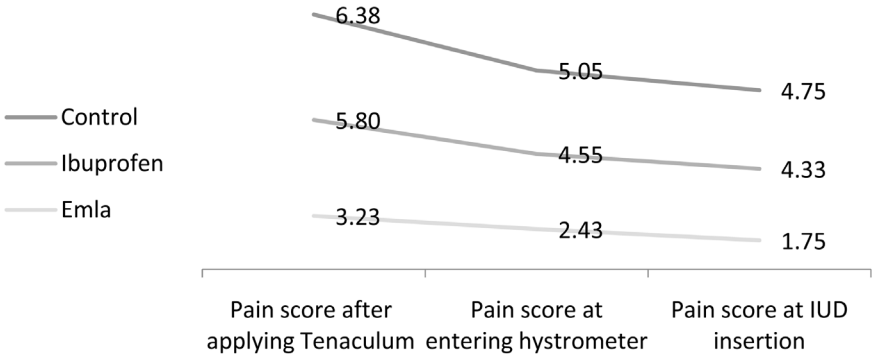

Figure 1. Pain reduction pattern of IUD inserting in three groups of participants.

4. Discussion

As IUD is an effective and acceptable method of contraception, several studies have been conducted about reducing the pain during insertion of IUD. Most of the studies conducted in this regard have examined the effect of chemical drugs like ibuprofen, naproxen, vitamin B1, misoprostol and herbal drugs such as lavender and a few of studies have been conducted on the effect of using topical and regional anesthesia on pain at the time of IUD insertion. In a study conducted by Alizadeh *et al.* (2010) and Nicholas *et al.* (2012) which entitled the effect of lidocaine gel on the pain caused by insertion of IUD, significant difference was not observed between lidocaine gel and placebo [7] [18]. Some of the reasons that can be involved in these results include the use of low concentration of anesthetic material, low durability of cream on cervix before procedure (1 minute), and lack of anesthetic material diversity. In the current study, the effect of EMLA cream on cervix at three stages of insertion of IUD was examined. Results showed that applying Tenaculum on the cervix that is the most painful stage, reduced the pain of people who received EMLA cream compared to the ibuprofen and placebo groups ($p < 0.001$). The findings of the current study are in line with results of study conducted by Liberty *et al.* (2007) to examine the effect of EMLA cream on Hysterosalpingography pain [15] and with the results of the study conducted by Stigliano *et al.* (1997) that examined the EMLA cream effect in Hysteroscopy pain [19]. In addition, they were consistent with the study conducted by Zibert (2002) that examined the effect of EMLA cream on the pain caused by cervix area laser [13]. Additionally, the current study results are in line with the result of the study conducted by Ttavakollian *et al.* (2013) entitled as investigation of EMLA cream effect on the pain caused during the insertion of copper IUD [20]. Therefore, any manipulation of the cervix causes severe pain in uterine and the transfer of the pain from uterine and cervix is conducted through two paths. Sensory fibers move from the body of the uterus through the eleventh and twelfth thoracic nerve roots to the central nervous system, while the sensory nerves of the cervix transfer to the second or the third and fourth sacral nerves through the pelvic nerves. The possible mechanism of EMLA cream lies in blocking the pain transferred from the second, third and fourth sacral nerves. In addition, study conducted by Hubacher *et al.* (2006) on the pain

caused by insertion of IUD with taking ibuprofen [9] as well as the research conducted by Bednarek *et al.* (2010) on the pain caused by insertion of IUD with taking prophylactic ibuprofen [21] indicated that taking ibuprofen did not reduce the pain caused by IUD. These results are not in line with the findings of the current study. In addition, in a study conducted by Jafari *et al.* (2013) entitled the effect of Vitamin B1 on the pain caused by IUD, it was found that taking B1 reduced the pain caused by insertion of IUD and it increased the satisfaction of the users [22], which it is in line with our study. Investigations show that all IUDs stimulate the formation of prostaglandins in the uterus and they cause smooth muscle contraction. Therefore, the procedure of IUD insertion is painful and its insertion makes the cervix environment and channel involved. Using EMLA cream on cervix environment can reduce the pain in this area significantly with the mechanism of probably blocking of the second, third, and fourth sacral nerves.

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Patient Satisfaction in Croatian Nationwide Mammography Screening Program

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Abstract

Mammographic screening programs are essential in timely detection and effective treatment of breast cancer. Since 2006, Croatia implemented a national MSP which asks for a regular biannual mammography for all women 50 - 69 years of age. First-visit screening attendance in the country is estimated at 58.3% with the trend of gradually decreasing re-attendance rates. Since patient satisfaction with the screening procedure may influence subsequent adherence, this study aimed to assess patient satisfaction in order to predict and improve patient re-attendance rate, a first-time effort of such kind in Croatia. 201 random patients undergoing mammography screening procedure at four facilities in Croatia were asked to complete an anonymous questionnaire which specifically evaluated the following aspects of patient experience: patient attitude, facility surroundings, staff attitude and pre-examination information transfer, associated physical pain, psychological discomfort, and finally overall patient impressions and satisfaction. The majority of our examinees expressed high satisfaction with MSP and an intention to re-screen; patient attitude, facility environment and staff attitude were deemed overly positive, whereas the majority of patients estimated the physical and psychological pain associated tolerable. These results suggest that patient satisfaction is not a critical factor influencing future adherence rate in MSP, and other components of the program should be evaluated and improved.

Keywords

Croatian, Mammography, Screening Program, Patient Satisfaction

1. Introduction

Mammography (MG) plays a central role in the diagnosis of breast cancer (BC), the 2nd leading cause of cancer-related death in women. Mammographic screening

programs (MSP) are of essential importance in timely detection and effective treatment of BC [1] [2]. National MSP is a significant logistical, organizational and financial challenge, whose success depends highly on attendance rate. Since 2006 Croatian national MSP calls for a regular biannual mammography for all women 50 - 69 years of age. First-visit screening attendance in Croatia is estimated at 58.5% [3]. Subsequent women's re-attendance may be influenced by the experience and satisfaction with their previous examination [4] [5]. In order to predict and improve re-attendance rate many studies have demonstrated the importance of evaluating patient satisfaction [6] [7] [8] [9] [10]. Patient satisfaction may be assessed in terms of specific contributing factors such as ease of accessibility, facility and staff resources, pre-examination information transfer, and physical and psychological discomfort induced by the examination. A successful mammography examination should involve timely scheduling, clear pre-examination information on the benefits and precautions of the procedure, comfortable waiting and examination rooms, welcoming professional staff and an agreeable breast compression technique during the examination. Considering that high patient satisfaction with the procedure could improve patient adherence rate, which has been decreasing in recent years, we designed this study to assess patient experience in a sample of women participating in Croatian national MSP. A first-time effort of such kind in quality assurance/quality control activities, which have not been sufficiently and systematically implemented in Croatia, this assessment contributes to identifying possible organizational and logistic weaknesses and opportunities for improvement of the program.

2. Materials and Methods

The series consists of a sample of 201 women undergoing regular MSP in the period from January to May 2014, aged 50 - 69 (average 58) years. Ten women per day undergoing screening MG procedure were randomly chosen to be surveyed at 4 university hospitals, 1 county hospital and 1 secondary healthcare facility (Dom zdravlja) using an anonymous questionnaire completed immediately after the examination with the authors' assistance. Informed consent was obtained from the patients and approved by the ethics committee of the MSP. The questionnaire consisted of 40 questions covering the following specific categories: general patient profile, level of information before MG, ease of accessibility and comfortableness of the mammography facility, staff attitude towards the patient, patient impressions of the mammographer, physical discomfort and pain of the examination, associated psychological discomfort, post-examination impressions and general patient satisfaction with MG. Questions assessing patient attitudes utilized Likert's Scale of 5 possible answers (1-strongly agree, 2-partially agree, 3-neither agree nor disagree, 4-mostly disagree, 5-strongly disagree). Pain level was assessed by the Visual Analogue Scale (VAS) (0 = no pain, 10 = severe pain) [11]. The reliability of the questionnaire was first assessed by a pilot study of 20 women, after which the questions were revised and improved. The descriptive study design was estimated as having good reliability by a Cronbach's α

coefficient > 0.7.

3. Results and Discussion

Success of national MSP depends highly on patient adherence rate, which is closely associated with the experiences related to the screening procedure. Assessment of general and specific factors influencing patient experience helps recognize potential areas for improving patient satisfaction and future adherence. Specifically, this study evaluated patient attitude, facility surroundings, staff attitude and pre-examination information transfer, associated physical pain, psychological discomfort, and finally overall patient impressions and satisfaction.

Positive *patient attitude before the examination* contributes to later patient satisfaction with the process [12]. In our study, a great majority of patients (97.0%, 195) stated that they agree that MG is reliable in detection of BC, and have a positive attitude about the procedure, which may be the consequence of educational advertisement campaigns undertaken in recent years in the public media, and educational written materials received with the letter of invitation for mammography screening. The authors of the study had an opportunity to observe women sitting and chattering in waiting-rooms prior to official survey and observed spontaneous affirmative conversations among participants with little or no doubts about the accuracy of MG and radiation risks related.

The *environment of the mammographic screening facility* is a contributing factor in decreasing patient anxiety. Great majority (93.5%, 188) of our examinees found the environment of the waiting rooms pleasant, 57.2% (115) agrees that the examination room is pleasant, but 30.3% (61) of patients completely disagree about adequacy of privacy during the procedure. Pleasant and welcoming environment of the waiting and examination room positively affects patient satisfaction [13], and could be achieved even with minor modifications if the staff is aware of this issue. In some institutions surveyed in our study there were no separated cabins for undressing available, and women usually prepared for the examination within the examination room in the presence of the mammographer preparing MG equipment for the exposure. Such limited privacy may be unpleasant for the women undergoing screening. Although MG units are rarely located in underground floors of old hospital buildings with elevators reserved only for staff, and limited parking areas for customers, 65.6% (132) of examinees did not have difficulties arriving to the place of the examination, considering traffic accessibility, parking opportunities and infrastructural barriers. An important factor that limits attendance rate to MSP in sparsely populated rural areas of Croatia is the lack of regular public transportation (e.g. Lika region, small islands) which discourages women to attend, although engagement of mobile MG units visiting these areas partially solves the problem.

Positive *staff attitude and pre-examination information* transfer are important contributing factors to patient satisfaction. Negative experience regarding staff attitude has been shown to decrease overall patient satisfaction with the proce-

dure [14]. Insufficient knowledge and distrust about the examination have been associated with dissatisfaction [12]. Pleasant and knowledgeable staff [15], as well as extra time and patience spent in explaining the procedure could decrease anxiety and improve rescreening rate [16]. Verbal information preceding the examination decreases patient anxiety, particularly in first time participants [17]. 87.5% (176) of our participants are satisfied with the manner of reception immediately after the entry to the MG facility, believe they "had been given clear and adequate information regarding the benefits and cautions of the procedure", that "the examination had not been performed in a hurry", and that "the personnel did their best to make them feel comfortable". However, only 67.2% (135) states they have been explained that breast pain and tenderness may appear following the procedure which would not be a reason for concern. Moreover, a significant number of women (17.9%, 36) think that the staff failed to give a proper explanation about the pain during breast compression, which was expected from them.

Subjective *patient assessment of mammographer's professional skills* could have an impact on patient satisfaction, considering that the women have been invited to the procedure and expect a high service quality and professional courtesy. More than a half (51.3%, 103) of the patients had an impression that the person who performed the examination was insufficiently trained and professionally skilled for such a task. Some studies [12] have shown that such a perception is due to the inability of non-professionals to properly estimate professional skills of the staff. The objective reasons may include limited training of some mammographers, especially younger ones which participate in MSP for financial reasons outside of regular working hours, often fatigued after morning clinical duties; also overbooking of patients, usually done due to variable attendance can cause an unexpectedly high workload and the mammographers to be in a hurry. This finding requires more research, and efforts in additional education and licensing of mammographers participating in MSP is needed. In spite of the abovementioned women's subjective impressions, 89.6% (180) of them believe that MG has been technically adequately performed and accurate enough for BC detection.

Physical breast pain and discomfort during MG is a significant factor that may cause anxiety and dissatisfaction with the procedure, and various strategies for pain relief could be attempted. 60% (120) of our patients found the procedure mildly painful or even completely painless (scores 1 - 3 on a 10-point Visual Analog Scale (VAS)), a highly satisfactory result considering the age of participants, and limited technical skills of mammographers in some facilities. The usual breast compression force of 12 daN was comfortable for 46.3% (93) of the patients, whereas others would ask to decrease the compression force. Great majority of patients (88.5%, 178) claim that they completely understand the reasons why breast compression is required to achieve proper quality of images and to reduce breast radiation dose, whereas (19.4%, 39) of patients think that MG is an inherently painful examination; 8% (16) of patients consider the reason being

was the too small size of their breasts, and 7.5% (15) the too large size of their breasts.

In one study [18] applying 4% lidocaine gel prior to compression significantly reduced patient discomfort. The majority (80.1%, 161) of women in our study, however, considered administering some kind of pain relief before the examination (e.g. an anesthetic gel) completely unnecessary. Other studies proposed different strategies for reducing pain, including employing music for relaxation [19] or using breast cushions [20]. Breast support plate was experienced as too cold for 22.9% (46) of patients in our study.

Psychological impressions associated to MG procedure are related to the imaging technique itself (getting undressed, compression) and to the mammographer's social skills and communication ability, and significantly influences patient satisfaction. Majority of women in our series (87.6%, 176) have not experienced the procedure psychologically embarrassing or unpleasant, 74.6% (150) of women agrees that the personnel acted supportively and reassuring, and 85.1% (171) states that the staff approach was encouraging them for future re-screening. The possibility of recall for further testing after basic MG screening has been confirmed to increase patient anxiety [21] [22], but 80.6% (162) of our patients agree that they feel no anxiety waiting for their examination results and possible recall.

Overall satisfaction with the MSP was good in the vast majority of examinees ("completely satisfied" 65.6% (132), "satisfied" 26.9% (54)), and 87.6% (176) of them found the associated discomfort negligible compared to possible benefits of MG. Only 6.9% (14) of women found the overall experience more taxing than they expected. The most (93.1%, 187) of women claim their examination experience encourages them to re-screen, and would recommend other women to participate in MSP.

There are some limitations of the study concerning sample patient characteristics, influence of social desirability bias and non-assessment of some factors. Most of the patients have previously undergone MG has found them tolerable: 7.5% (15) underwent MG for the first time, 7.9% (16) previously underwent screening MG once, 17.4% (35) twice, and 64.2% (129) three or more times. A more appropriate assessment of screening experience would involve a greater number of first-time participants. The survey was completed in the examination facility, which could have the results affected by social desirability bias [23]. Most participants in the sample were urban-dwelling (81.6%, 111), were better educated (53.2% (107) were high-school educated and 14.4% (29) had only primary school), and had greater accessibility to MSP than residents of isolated rural communities. Some factors which could influence patient satisfaction, such as result reporting [24] and information environment [25] have not been assessed. Finally, this study did not account for the discrepancy between the intentions to re-screen and realized re-screening, an already documented phenomenon [14]. All these factors could overestimate the portion of satisfied participants and future patient adherence rate.

4. Conclusion

In conclusion, in this first quality assurance survey in Croatian MSP the majority of our examinees expressed high satisfaction with MSP and an intention to re-screen. More specifically, patient attitude, facility environment and staff attitude were deemed overly positive, whereas the majority of patients estimated the physical and psychological pain associated tolerable. The results of this study suggest that patient satisfaction would not be a critical factor influencing future adherence rate in MSP, and other components of the program should be improved to maintain satisfactory participation.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

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

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A Study of Cardiac Profile in Patients with Snake Envenomation and Its Complications

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Abstract

Background: Snake bite is a common and frequently devastating environmental and occupational disease, especially in rural areas of tropical developing countries. The present study was undertaken to evaluate the effect on cardiac profile in patients with snake envenomation and its complications. **Methods**: A total of 200 patients with snake envenomation were enrolled in this study excluding patients having history of any cardiovascular disease, renal disease, coagulopathy, liver disease, neuromuscular disease and those cases who bitten by non-poisonous snakes. All patients underwent physical examination, laboratory, Electrocardiogram (ECG), X-ray of chest and echocardiogram investigations. **Results**: A total of 200 cases had envenomation having 116 (58%) of male subjects. Most common local signs were edema 187 (93.5%), tenderness 141 (70.5%), skin necrosis 81 (40.5%) and blistering 12 (6%). Severity of local envenomation was graded into mild 66 (33%), moderate 120 (60%) and severe 14 (7%) cases. Systemic manifestations were present in 83 patients of venomous bites. It includes that majorly 53 (26.5%) cases had vomiting, 44 (22%) cases had abdominal pain and 9 (4.5%) cases of hypotension. ECG manifestation showed 27 (13.5%), 6 (3%) and 1 (0.5%) patients had sinus tachycardia, sinus bradycardia and ventricular tachycardia respectively. While, 9 (4.5%) cases had T inversion alone in precordial leads. Mortality (3%) was observed in intracranial bleed, neurotoxicity and capillary leak syndrome. However, cardiovascular involvement was not responsible for mortality in any cases. **Conclusion**: In conclusion, ventricular tachycardia is one of the manifestations of snake envenomation. Moreover, sinus tachycardia is common cardiovascular sign which may not be due to cardiac causes. Mortality results conclude that, cardiovascular involvement could not be responsible for mortality in snake envenomation.

Keywords

Snake Envenomation, Cardiac Complications, Sinus Tachycardia

1. Introduction

Snake bite is one of the major public health problems especially in tropical and subtropical countries. Snake bite is a common medical emergency encountered in the tropics and an estimated 35,000 - 50,000 people die of snake every year in India. Approximately 15% of 3000 species of snakes found worldwide are considered to be dangerous to humans. Among those species 52 poisonous species found in India, majority of bites and consequent mortality is attributable to 5 species viz. *Ophiophagus hannah* (king cobra), *Naja naja* (common cobra), *Daboia ruselli* (Rossell's viper), *Bungarus caeruleus* (krait) and *Echis carinatae* (saw-scaled viper). In Kerala, around 104 species are known, of which 37 are poisonous [1] [2] [3].

Snake venom is probably the oldest known poison to mankind and has been described in oldest medical books and myths. The snake venom contains many enzymes like digestive hydrolases, hyaluronidase, and activators or inactivators of physiological processes which include L-amino acid oxidase, phosphomono and diesterase, 5'-nucleotidase, DNAase, NAD-Nucleosidase, phospholipase A2, and peptidases. Also contains non enzymatic proteins and polypeptides. Among non enzymatic proteins, hemorrhagins, neurotoxins and cardiotoxins are important. Hemorrhagins are present mainly in *Echis carinatus*. Haemorrhage, shock and acute renal failure are the main causes of death in cases of elapid bite [4] [5]. Cardiotoxicity is also seen in many cases dying of severe viper bite. This may occur in the form of sudden hypotension, cardiac arrhythmia, myocardial infarction and changes in the electrocardiogram mainly of ST segment and T wave. Many cases of myocardial infarction following snake bite have been reported [6] [7]. Coronary angiogram showed normal coronaries except in case where segmental contraction of coronaries was present. A case of second degree atrioventricular block has been reported [8]. In addition to this there may be pulmonary edema and alteration in enzymes like serum aspartate (SGOT) and creatine phosphokinase [5].

Mechanism of cardiotoxicity includes direct toxic effect on the myocardium, coagulation abnormalities and vasopasm induced by hemorrhagins or endothelins contained in the venom of some snakes [9]. Causes of hypotension and shock include hypovolemia, vasodilatation, and myocardial dysfunction. Moreover, bradykinin prolongs hypotensive effect by inactivating the peptidyl dipeptisase responsible both for destroying and for converting angiotensin I to angiotension II. This observation led to the synthesis of angiotensin-converting enzyme inhibitors (ACEI). Bradykinin-potentiating and ACE-inhibiting peptides have also been found in a number of other crotaline venoms [10] [11]. So far, least work has been done in India on complications and cardiotoxicity profile

following poisonous snake bite. Therefore, present study was undertaken to find out the effect on cardiac profile and complications in the victims of snake envenomation.

2. Methods

2.1. Patient Population and Study Design

The prospective study was conducted in 200 patients of snake envenomation. Snake bite victims admitted to Government Medical College, Kottayam, Kerala, India from May 2005 to August 2006 were included in this study. Those patients had definite evidence (sign and symptoms) of snake envenomation were enrolled. While, those patients having history of any cardiovascular disease, renal disease, coaglulopathy, liver disease and liver muscular disease were excluded from this study. In addition, those cases who bitten by non-poisonous snakes were also excluded. All recruitments were conducted after obtaining informed written consent who qualifies the selection criteria.

All patients underwent physical examination, routine and specific laboratory investigation pertaining to snake envenomation. Moreover, specific cardiac profile determined by 12 lead Electrocardiogram (ECG), X-ray of chest and echocardiogram in all patients. Severity of bite was classified according to criteria suggested by Ramming with some modification by Saini *et al.* (1984) [12]. The details severity based classification depicted in Table 1. The treatment was given as per WHO guidelines. The initial dose of polyspecific antisnake venom was given as 100 cc without any change in dose for adults or children. Secondary dose can be given with 20 to 50 cc at interval of 2 - 6 h. Patients were continuously monitored for the development of any complication and were managed accordingly.

All investigations were conducted in conformity with ethical principles of research and according to guideline of declaration of Helsinki and approved by the ethical review board of the institution.

Table 1. Scoring classification based on severity of sign and symptoms in patients of snake envenomation.

	Local	Systemic	Coagulation
Minimal	Swelling, erythema or ecchymoses confined to site of bite	No coagulation signs or symptoms	No coagulation abnormalities or other important laboratory abnormalities
Moderate	Progress of swelling, erythema or ecchymosis beyond the site of bite	Non life threatening signs and symptoms (Nausea, vomiting, perioral paraesthesia, myokymia & mild hypotension)	Mildly abnormal coagulation profile, clinically significant bleeding and mild abnormalities on other tests
Severe	Rapid swelling, erythema or ecchymosis involving the entire body part	Markedly severe signs and symptoms (hypotension–SBP < 90 mmHg, altered sensorium, tachycardia, tachypnoe and respiratory distress)	Markedly abnormal coagulation profile with evidence of bleeding or threat of spontaneous hemorrhage, (unmeasurable INR, a PTT & fibrinogen and severe thrombocytopenia < 20,000/cmm)

2.2. Statistical Analysis

Patient baseline characteristics and procedural data were presented as frequency and percentages. In case of normal distribution, data presented as mean ± SD while non-normal distribution data were presented as median (interquartile ranges).

3. Results

3.1. Participant's Basic and Demographic Characteristics

A total of 586 patients with suspected snake bites admitted to Pariyaram Medical College, Kannur, Kerala during study period. Out of these 586 patients, 200 cases had envenomation having 58% of male subjects. The age group most affected was 31 - 50 years (52%). Majority (76.6%) of cases of snake bite came to the hospital within 24 hours of bite while 40% reported within the first 12 hours. Venomous bite occurred in 93% of subject outdoor whereas, 7% patients were victim of indoor bites. Accidental bites occurs to 98.5% patients and rest 1.5% are snake charmers (occupation bites).In addition, site of bite at lower limb (81%) is much more than upper limb (19%).Whereas, no bites were observed over face or other part of body. All baseline characteristics of envenomated patients are depicted in Table 2.

Table 2. Baseline characteristics of envenomated patients.

Variable	
Total number of subjects, n	200
Female, n (%)	84 (42%)
Age, median	Median 40 (4 - 60)
Location and type of Bite	
Outdoor bites, n (%)	186 (93%)
Indoor bites, n (%)	14 (7%)
Accidental bites, n (%)	197 (98.5%)
Occupational (snake charmer) bites, n (%)	3 (1.5%)
Site of Bite	
Lower limb, n (%)	162 (81%)
Upper limb, n (%)	38 (19%)
Rest of Body, n (%)	0 (0%)
Type of snakes	
Viper, n (%)	65 (32.5%)
Cobra, n (%)	3 (1.5%)
Krait, n (%)	1 (0.5%)
Unknown, n (%)	131 (65.5%)

3.2. Clinical Manifestations

Local envenomation: signs and severity

Fang mark was present in 107 cases which constituted about 53.5% of venomous bites and 93 patients had no definite fang mark. Most common local sign was edema (93.5%), tenderness (70.5%), skin necrosis (40.5%) and blistering (6%). Severity of local envenomation was assessed by presence and extends of local edema which graded into mild (33%), moderate (60%) and severe (7%) cases.

Systemic manifestation:

Systemic manifestations were present in 83 patients of venomous bites. It includes majorly 53 cases had vomiting, 44 cases had abdominal pain and 9 cases of hypotension. Moreover, one patient suffered with cardiac arrhythmia. The patient presented with a sustained monomorphic ventricular tachycardia (VT) at the rate of 180/minute but did not have hypotension treated with i.v. amiodarone and not require cardioversion. Echocardiogram was normal with left ventricular function. It may be incidental cardiac arrhythmia or complication of snake envenomation but seen only in 0.5% of patients. Details systemic manifestation is depicted in Table 3.

Table 3. Clinical course of envenomated patients.

Variable	
Local Signs	
Definite fang mark, n (%)	107 (53.5%)
Undefinite fang mark, n (%)	93 (46.5%)
Edema, n (%)	187 (93.5%)
Tenderness, n (%)	141 (70.5%)
Skin necrosis, n (%)	81 (40.5%)
Blistering, n (%)	12 (6%)
Severity of Envenomation	
Mild, n (%)	66 (33%)
Moderate, n (%)	120 (60%)
Severe, n (%)	14 (7%)
Systemic manifestation	
Vomiting, n (%)	53 (26.5%)
Abdominal Pain, n (%)	44 (22%)
Oliguria/anuria, n (%)	14 (7%)
Hypotension, n (%)	9 (4.5%)
Bleeding manifestation, n (%)	8 (4%)
Neurological symptoms, n (%)	6 (3%)
Presyncope/syncope, n (%)	4 (2%)
Cardiac arrhythmia, n (%)	1 (0.5%)

3.3. Laboratory Investigations

Basic blood investigation were done along with bedside monitoring of clotting time, coagulation parameter like prothrombin time and activated partial thromboplastin time (PTT). Results suggest that, 127 patients have clotting time above the cut off value *i.e.* 20 minutes. Moreover, 104 patients showed cut off time greater than 10 second for PTT. Regarding low platelet count, 15 patients out of 76 patients (19%) had severe thrombocytopenia (<50,000) requiring platelet transfusion. Routine and other specific laboratory investigation were depicted in Table 4.

3.4. Electrocardiogram Examinations

ECG manifestation showed 27 cases had sinus tachycardia, 6 patients had sinus bradycardia. While 9 cases had T inversion alone in precordial leads. Detail of changes were observed in the ECG were represented in Figure 1.

Table 4. Initial laboratory findings of snake envenomated patients.

Parameters	Cut of Value	Number of patients	
		Normal	Abnormal
Hemoglobin	>13.5 g/dl in males >12 g/dl in females	142	58
Total leukocyte count	<11,000/cmm	140	60
Platelet count	>100,000/cmm	124	76
Blood urea	<40 mg/dl	149	51
Serum creatinine	<1.4 mg/dl	149	51
Clotting time	>20 minutes	73	127
Prothombin time	>15 seconds	74	126
Activated PTT time	>10 seconds	96	104

PTT: Partial thromboplastin time.

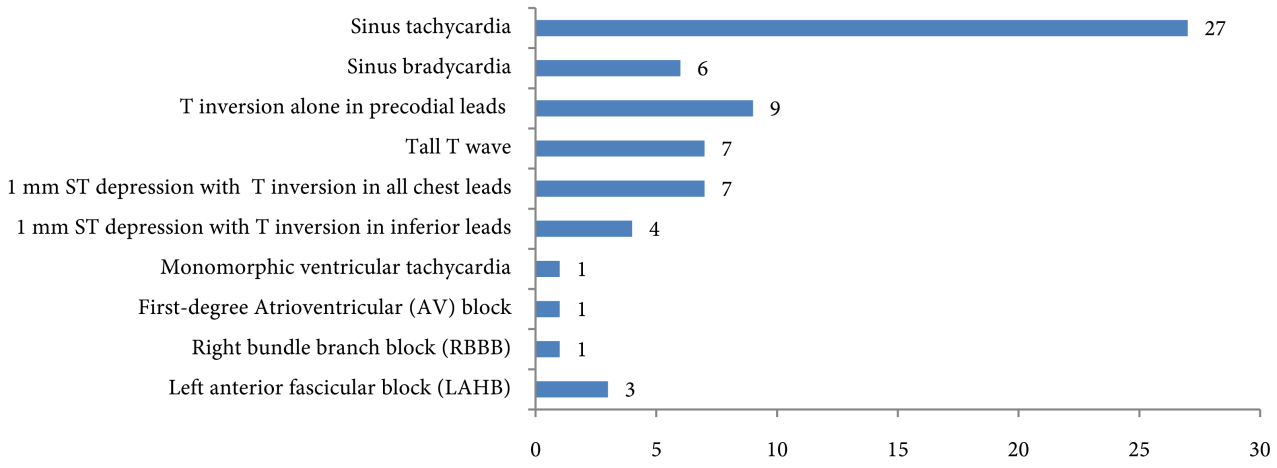

Figure 1. Changes observed during electrocardiogram examination of snake envenomated patients.

3.5. Echocardiogram Investigation

Echocardiographic finding were within normal limit in all patients except 3 patients who had asymmetrical septal hypertrophy as an incidental finding. Patients with ventricular tachycardia had good ventricular function.

3.6. Complications

A total of 79 patients had represented with at least single complication. Table 5 represents the most common complications were acute renal failure in 51 patients and 39 cases of Intra vascular haemolysis. Compartment syndrome, secondary infection and unexplained hypotension were observed in 4 (2%), 5 (2.5%) and 8 (4%) patients. One case had ventricular tachycardia with no risk for coronary artery disease, which is reverted to normal sinus rhythm with direct current (DC) cardioversion followed by anti snake venom. This patient with ventricular tachycardia had good ventricular function.

3.7. Laboratory Investigations

Mortality

Mortality was observed in 6 cases of total venomous bites patients (Figure 2). Mortality was observed in intracranial bleed, neurotoxicity and capillary leak syndrome. Clinically, neurotoxicity was assessed by testing for muscle power and for adequacy of ventilatory function. However, cardiovascular involvement was not responsible for mortality in any cases.

4. Discussion

This study on the profile of cardiovascular complications due to snake bite was carried out with a view to observe the changes in cardiovascular system. A total of 200 subjects with venomous bites were studied. There were 116 males and 84 females with ratio of 1.4:1.

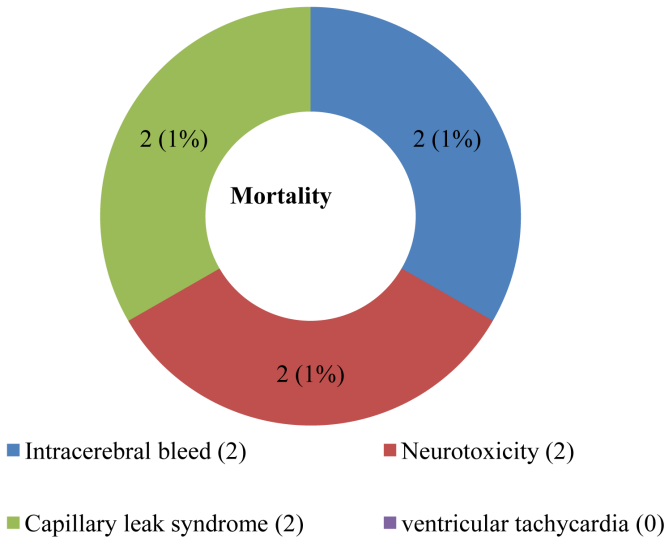

Figure 2. The effect on mortality in snake envenomated patients.

Table 5. Different complications in snake envenomated patients.

Complications	Patients
Acute renal failure	51 (25.5%)
Intra vascular haemolysis	39 (19.5%)
Unexplained hypotension	8 (4%)
Secondary infection	5 (2.5%)
Compartment syndrome	4 (2.0%)
Intra cerebral bleed	4 (2.0%)
Neurotoxicity	2 (1.0%)
Ventricular tachycardia	1 (0.5%)
Capillary leak syndrome	2 (1.0%)

Systemic manifestations were present in 83 patients (41.5% of venomous bites). Most common manifestation noted was vomiting which was present in 26.5% patients. Prolonged clotting time was the commonest manifestation of systemic toxicity in haemotoxic snake bites. In addition, Pain abdomen was present in 22% and 7% patients had renal manifestation in the form of oliguria/anuria, hypotension was noted in 4.5% of venomous bites. Moreover, 2% patients with presyncope/syncope and 4 cases presented in a coma state due to intra cerebral bleed secondary to haemotoxic envenomation. One patient presented with palpitation due to ventricular tachycardia which reverted to normal with DC shock followed by antisnake venom administration. Nayak *et al.* (1990) showed 25% of cardiotoxicity among viperine bite [3]. In our study, cardiac involvement as evidenced by electrocardiographic changes which reverted to normal was present in 31.5% of patients. Out of this only one patient had serious complication like ventricular tachycardia. Most common cardiac manifestation was sinus tachycardia which was present in 27 patients. Even though there are earlier reports of myocardial infarction [7] [13], none of our patients had ST elevation in electrocardiogram suggestive myocardial infarction. Eleven patients had ST depression in either anterior or inferior leads which might be due to coronary artery involvement or myocartitis. None of our patients had chest pain even though ECG showed changes like ST depression. Previous reported cardiotoxicity in 7% cases or elapide bite and none in viper bite case [14]. None of the patients in our study had features of pulmonary edema. Features of peripheral circulatory failure were present in 4% patients who responded to antisnake venom, volume replacement and inotropes.

In the present study, heart rate disturbance was present in 16.5 percent out of which 13.5% had tachycardia and 3% had bradycardia. This finding is almost reverse of the observation of Reid *et al.* (1975) [5]. In patients who had tachycardia without other ECG changes, heart rate returned to normal in 12 - 20 hours. Tachycardia was probably because of shock, fever or acute blood loss. However, bradycardia may occur due to direct depressant action of snake venom over sinoatrial node. Rhythm disturbance in the form of ventricular tachycardia was

seen in 1 patient of our series. Ventricular tachycardia as a presentation of snake envenomation has been reported earlier [15].

Eight patients had unexplained hypotension (4%) and none of the patient had hypertension. These observations are similar to those of previous literature. Hypertension has noted in patients with snake bite, which was probably psychogenic in origin which is a well known factor in producing hypertension. The possible mechanisms responsible for hypotension could be excessive blood loss as bleeding tendency was seen in 63% patients in our study and vasovagal syncope after snake bite or bradykinin induced vasodilation [16]. None of the patient had pulmonary edema. However, previously pulmonary edema was reported in 6.6% of snake envenomated patients by Nayak *et al.* (1990) [3].

Our results reflect, abnormality in ECG was found in 31.5% patients. Most of these appear to be due to sinus tachycardia, which may be related to the stress of illness or being hospitalized, and may make the rate of "abnormality" seem high. However, this incidence differs from the reported observations of Reid who reported an abnormal ECG in 2% cases [5]. Ischaemic changes like ST depression were seen in 5.5% cases which reverted to normal within 3 - 4 days. These ECG changes can be explained by two possibilities; one is that changes in ST-T segment because of thrombosis or sub-intimal haemorrhage in coronary vessels. Snake venom causes disseminated intravascular coagulation which can lead to thrombosis or sub-intimal haemorrhage in coronary arteries and produces ECG changes. Another possibility may be direct toxic effect of venom on heart which may likely give an explanation for sinus bradycardia, arrhythmias and atrioventricular block [17].

In addition, mortality was 3% which is varies from previous literature, as 10% and 1.96% mortality were observed by Nayak *et al.* (1990) and Bhat *et al.* (1974) [3] [18]. All those patients had severe envenomation and late hospitalization. Also, they were in shock, and some may had massive bleeding. Cardiovascular complication was not responsible for mortality in any of the cases.

5. Limitations of the Study

Being a tertiary care center, study may not be real reflection of the original magnitude of the problem in the community. Moreover, majority of the study groups were haemotoxic bites and the number of elapid bites was very small in the study group. However, there were no long term follow up of the patients who showed ECG abnormalities.

6. Conclusion

Overall analysis of results suggests that, cardiac involvement is uncommon in snake envenomation. As occurrence of sinus tachycardia in snake envenomation was most likely due to non-cardiac causes. Mortality results suggest that, cardiovascular involvement may not be responsible for mortality in snake envenomation.

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Hyperuricemia as a Predictor of Progression of Chronic Kidney Disease: A Matched Cohort Analysis

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Abstract

Background: The clinical significance of uric acid (UA) in patients with chronic kidney disease (CKD) has never been elucidated in detail. **Objectives:** The aim of this study was to elucidate the predictive value of hyperuricemia (HU) in relation to kidney disease progression in CKD patients. **Methods:** We reviewed data obtained from 201 CKD patients. Renal outcome was assessed by performing the Kaplan-Meier and Cox proportional hazard regression models. The renal outcomes of CKD patients with and without HU were compared by using a propensity score-matched cohort. **Results:** The results of a multivariate Cox regression analysis showed that HU (UA ≥ 7.1 mg/dL) (P = 0.001), diabetes mellitus (P = 0.003), and a high urine albumin-to-creatinine ratio (P = 0.0005) were significantly associated with a ≥50% eGFR decline or ESRD. The serum UA values were positively correlated with mean blood pressure (P = 0.007), visceral fat area (P = 0.0003), and maximum carotid intima-media thickness (P = 0.0003). The Kaplan-Meier analysis in the propensity score-matched cohort indicated that the renal survival rate of the group of CKD patients with HU was significantly lower than that of the group without HU (log rank, P < 0.0001), even after complete adjustment for the eGFR. **Conclusion:** The results of this study suggest that the serum UA value is a predictor of CKD progression.

Keywords

CKD, Hyperuricemia, Propensity Score Matching, Visceral Fat Area, Maximum Carotid Intima-Media Thickness

1. Introduction

Chronic kidney disease (CKD) is affected by multiple risk factors for disease progression [1] [2], and it is extremely important to identify risk factors for the acceleration of the CKD progression. The impact of the serum uric acid (UA) on renal prognosis of CKD patients has recently been attracting attention [3], and our group has reported finding that the serum UA value can serve as a predictor of progression of kidney disease in biopsy-proven nephrosclerosis patients [4]. However, because the serum UA elevation due to the decreased renal UA clearance in CKD patients makes it difficult to assess the role of UA in the progression of CKD, the predictive value of UA in regard to the progression of CKD remains a matter of controversy [5]-[11].

A high serum UA level is associated with obesity [12] [13] and is a risk factor for carotid atherosclerosis [14]. The aim of the present study was to elucidate the predictive value of hyperuricemia (HU) in relation to kidney disease progression in CKD patients.

2. Methods

2.1. Patient Selection

Abdominal computed tomography (CT) and carotid ultrasonography were performed on 201 CKD outpatients who attended the Kidney Center of Tokyo Women's Medical University Hospital between August 2006 and August 2007. CKD was diagnosed according to previously described criteria [15]. Among these 201 patients, the following patients were excluded from participation: 1) patients who had been treated with antihyperuricemic agents; 2) patients with no UA data. The remaining 122 patients were ultimately enrolled as subjects of the present study (**Figure 1**).

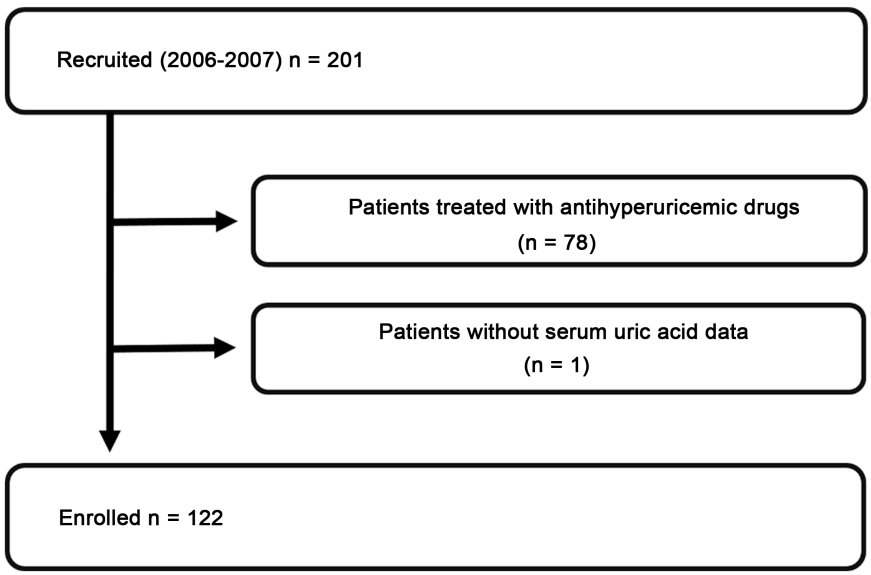


Figure 1. Flow chart of patient selection. The 79 patients who did not meet the entry criteria were excluded from the 201 patients screened, and the other 122 patients were enrolled in this study.

The subjects' human rights and method of protecting personal information were well considered. All of the relevant and responsible staff adhered to the Helsinki Declaration (amended October 2013) and the Ethical Guidelines for Clinical Studies (revised July 31, 2008, referred to hereafter as the Clinical Studies Ethical Guidelines) in the execution of this study. The study was approved by the Medical Ethics Committee of Tokyo Women's Medical University (#4188). All participants gave their informed consent to participate in the study.

2.2. Measurements of Covariates

At a regular ambulatory visit, each subject underwent anthropometric and physical examinations that included blood pressure (BP), height, body weight, visceral fat area (VFA), subcutaneous fat area (SFA), and maximum carotid intima-media thickness (IMT). BP was measured in triplicate with a mercury sphygmomanometer, and the average value was used in the analysis. VFA and SFA were measured by CT, and IMT was measured by carotid ultrasonography. Details of the measurement techniques are described below in this section. All biochemical analyses were performed on samples obtained from fasted subjects. Serum creatinine (Cr) levels were measured enzymatically. The estimated glomerular filtration rate (eGFR) was calculated by using the previously described formula for Japanese patients [16]. Urinary albumin was measured by a latex agglutination test [17]. Urinary albumin excretion was expressed as the urine albumin-to-creatinine ratio (UACR). We also assessed the impact of concomitant drug use and comorbidities at entry [18] [19]. The concomitant drugs being taken by the patients were: antihypertensive drugs, diuretics, and drugs for the treatment of hyperuricemia, dyslipidemia, and diabetes mellitus.

The baseline parameters assessed in this study were: age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), BMI, VFA, SFA, IMT, eGFR, hemoglobin, serum albumin, UA, total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglyceride (TG) values, and UACR. Comorbidities are defined below. The subjects were followed up until July 2016.

2.3. Abdominal CT Examination

The multi-slice CT examination was performed by using a GE Light Speed. An index image was obtained before scanning, and the umbilicus to L4-5 level was identified [20] [21]. VFA at this level correlated extremely well with whole intra-abdominal fat content ($r = 0.94$). Horizontal images were obtained at 400 mA and 120 kVp with a scan time of 1.0 s. The range of CT values covered optimal CT numbers for fat tissue, *i.e.*, from −150 to −40.14 Data were stored and analyzed with GE advantage workstation Ver.4.0.

2.4. Carotid Ultrasonography

An experienced examiner blinded to the patient data performed high-resolution duplex carotid ultrasonography with a 7.5-MHz duplex scanner (Aplio XG; To-

shiba, Tokyo, Japan). The common and internal carotid arteries were scanned cross-sectionally and longitudinally to estimate the presence and distribution of atherosclerotic plaques. The entire length of both common carotid arteries and both internal carotid arteries up to approximately 20 mm distal to the tip of the carotid bifurcation were scanned. Maximum intima-media thickness (IMT) measurements were obtained to identify the thickest region of the arterial wall according to an international consensus report [22].

2.5. Definition of Comorbidities

Hypertension: Being treated with an oral antihypertensive agent, SBP ≥ 140 mmHg, DBP ≥ 90 mmHg.

Hyperuricemia (HU): Being treated with an oral antihyperuricemic agent, serum UA level ≥ 7.1 mg/dL.

Hypercholesterolemia: Being treated with an oral antidyslipidemic agent, serum TC level ≥ 220 mg/dL, or serum LDL level ≥ 140 mg/dL.

Hypertriglyceridemia: Being treated with an oral antidyslipidemic agent or serum TG level ≥ 150 mg/dL.

Diabetes mellitus: Being treated with an antidiabetic agent or a history of diagnosis with diabetes mellitus.

2.6. Outcome Evaluation (Endpoint)

The outcome variable of interest was kidney disease progression, which was defined as a ≥50% decline in eGFR from baseline (≥50% eGFR decline) or ESRD requiring dialysis.

2.7. Statistical Analysis

Continuous variables are reported as the mean ± standard deviation (SD), and categorical variables are reported as percentages unless otherwise stated. We compared participant outcomes by performing an unpaired *t*-test or chi-square test, or Fisher's exact test. The correlations between UA and the other variables were assessed by using Pearson's correlation coefficients. The optimal cut-off serum UA value for discriminating ≥a 50% eGFR decline or ESRD during follow-up examinations was determined by performing a receiver operating characteristic (ROC) analysis. The patients were divided according to their UA level at baseline into an HU group, *i.e.*, a group whose UA value was ≥7.1 mg/dL, and a non-HU group, *i.e.*, a group whose UA value was <7.1 mg/dL. Prognostic variables for renal outcome were assessed by the univariate and multivariate Cox proportional hazards method. We included covariates for age, sex, VFA, IMT, eGFR, UACR, and comorbidities, including HU, at baseline in the Cox proportional hazards models. Variables with *P*-values less than 0.1 in the univariate model were included in the multivariate model. Renal outcome which was a ≥50% eGFR decline or ESRD, and interval estimates between the HU group and the non-HU group was calculated by the Kaplan–Meier method and evaluated by the log-rank test.

To further assess whether associations were consistent across clinically matched subgroups, we fit propensity score-matched models that included several potential modifying variables (sex, eGFR, MBP, VFA), and performed subgroup analyses of the groups. The caliper-matching method was used with a maximum tolerance level of 0.1. Standardized differences were calculated to assess the appropriateness of matching, and 95% confidence intervals (CIs) were calculated. *P* values <0.05 were considered statistically significant. All statistical analyses were performed by using the JMP Pro ver.12.1.0 software program (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients

The 122 subjects consisted of 48 males and 74 females, and their mean age at baseline was 58.7 ± 13.9 years (range 24 - 84 years). The mean SBP was 124.9 ± 8.1 mmHg, DBP 76.4 ± 6.2 mmHg, MBP 92.6 ± 6.6 mmHg, BMI 23.9 ± 4.1 kg/m^2, VFA 117.1 ± 62.1 cm^2, IMT 1.44 ± 0.81 mm, UACR 238.7 ± 548.1 mg/g Cr, and eGFR 63.7 ± 19.8 mL/min/1.73 m^2. The concomitant drug data showed that 75 subjects were being treated with an antihypertensive agent, 43 with an antidyslipidemic agent, 17 with an antidiabetic agent, 20 with a corticosteroid, 7 with an immunosuppressing agent, and 19 with a diuretic. The comorbidity data showed that 76 patients had hypertension, 20 had HU (UA ≥ 7.1 mg/dL), 73 had hypercholesterolemia, 78 had hypertriglyceridemia, and 26 had diabetes mellitus. The overall follow-up period was 8.3 ± 2.4 years, and 16 patients had reached the endpoint (≥50% eGFR decline or ESRD) during the follow-up period.

3.2. Serum UA Cut-Off Value as a Predictor of Kidney Disease Progression

We performed ROC analyses to identify the optimal UA cut-off value for discriminating a ≥50% eGFR decline or ESRD during the follow-up examination, and the results showed that it was 7.1 mg/dL (AUC = 0.74, sensitivity = 62.5%, specificity = 90.6%, Figure 2).

3.3. Comparison between the Clinical Findings According to Serum UA Value Groups in the Total Cohort

We compared the clinical characteristics of the two groups established according to UA value at baseline (Table 1). The baseline serum UA (7.8 ± 0.6 vs. 5.0 ± 1.2 mg/dL, $P \leq 0.0001$), SBP (130.0 ± 7.8 vs. 123.9 ± 7.8 mmHg, $P = 0.002$), DBP (80.5 ± 5.2 vs. 75.6 ± 6.1 mmHg, $P = 0.001$), MBP (97.0 ± 5.9 vs. 91.7 ± 6.4 mmHg, $P = 0.0009$), VFA (158.8 ± 75.4 vs. 108.9 ± 56.0 cm^2, $P = 0.0008$), and UACR (649.7 ± 1035.8 vs. 158.1 ± 343.6 mg/g Cr, $P = 0.0002$) values of the HU group were significantly higher than in the non-HU group, and the eGFR (43.8 ± 19.0 vs. 67.6 ± 17.6 mL/min/1.73 m^2, $P \leq 0.0001$) and HDL-C (51.3 ± 15.5 vs. 60.7 ± 16.8 mg/dL, $P = 0.02$) values of the HU group were significantly lower

Table 1. Patient characteristics according to baseline serum uric acid levels (total cohort n = 122).

Variables	Total cohort			*P*-value	Standardized Differences
	Total	HU (UA ≥ 7.1 mg/dL)	Non HU (UA < 7.1 mg/dL)		
	n = 122	n = 20	n = 102		
Clinical Findings					
Age (years)	58.7 ± 13.9	59.8 ± 14.0	58.4 ± 13.9	0.7	0.100
Gender (Male; %)	39.3	70.0	33.3	0.002	0.790
SBP (mmHg)	124.9 ± 8.1	130.0 ± 7.8	123.9 ± 7.8	0.002	0.782
DBP (mmHg)	76.4 ± 6.2	80.5 ± 5.2	75.6 ± 6.1	0.001	0.865
MBP (mmHg)	92.6 ± 6.6	97.0 ± 5.9	91.7 ± 6.4	0.0009	0.861
BMI (kg/m^2)	23.9 ± 4.1	25.5 ± 5.8	23.6 ± 3.7	0.06	0.391
Visceral fat area (cm^2)	117.1 ± 62.1	158.8 ± 75.4	108.9 ± 56.0	0.0008	0.751
Subcutaneous fat area (cm^2)	184.5 ± 94.3	212.4 ± 146.1	179.1 ± 80.3	0.1	0.282
IMT(mm)	1.44 ± 0.81	1.75 ± 1.02	1.38 ± 0.76	0.1	0.411
Laboratory Findings					
Serum Albumin (g/dL)	4.2 ± 0.3	4.1 ± 0.4	4.2 ± 0.3	0.1	0.283
Hemoglobin (g/dL)	13.5 ± 1.5	12.9 ± 2.1	13.6 ± 1.4	0.1	0.392
eGFR ($mL/min/1.73\ m^2$)	63.7 ± 19.8	43.8 ± 19.0	67.6 ± 17.6	<0.0001	1.300
Uric Acid (mg/dL)	5.5 ± 1.5	7.8 ± 0.6	5.0 ± 1.2	<0.0001	2.951
Total Cholesterol (mg/dL)	211.9 ± 49.3	213.4 ± 46.7	211.6 ± 50.0	0.9	0.037
LDL Cholesterol (mg/dL)	124.4 ± 44.7	131.0 ± 34.5	123.1 ± 46.5	0.5	0.193
HDL Cholesterol (mg/dL)	59.2 ± 16.9	51.3 ± 15.5	60.7 ± 16.8	0.02	0.582
Triglyceride (mg/dL)	141.2 ± 71.4	155.7 ± 64.5	138.3 ± 72.6	0.3	0.253
UACR (mg/g Cre)	238.7 ± 548.1	649.7 ± 1035.8	158.1 ± 343.6	0.0002	0.637
Concomitant drugs					
Antihypertensive agents (%)	61.5	70.0	59.8	0.4	0.215
Antidyslipidemic agents (%)	35.3	35.0	35.3	1.0	0.006
Antidiabetic agents (%)	13.9	30.0	10.8	0.02	0.491
Corticosteroids (%)	16.4	15.0	16.7	0.9	0.047
Immunosuppressing agents (%)	5.7	5.0	5.9	0.9	0.040
Diuretics (%)	15.6	20.0	14.7	0.6	0.140
Comorbidities					
Hypertension (%)	62.3	70.0	60.8	0.4	0.194
HU (UA ≥ 7.1 mg/dL) (%)	16.4	100.0	0.0	<0.0001	-
Hypercholesterolemia (%)	59.8	55.0	60.8	0.6	0.118
Hypertriglyceridemia (%)	63.9	65.0	63.7	0.9	0.027
Diabetes mellitus (%)	21.3	35.0	18.6	0.1	0.377

Continuous values are expressed as means ± standard deviation. Count data are expressed as percentages. Abbreviation: n, number; HU, Hyperuricemia; UA, Uric Acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index; IMT, maximum carotid intima-media thickness; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

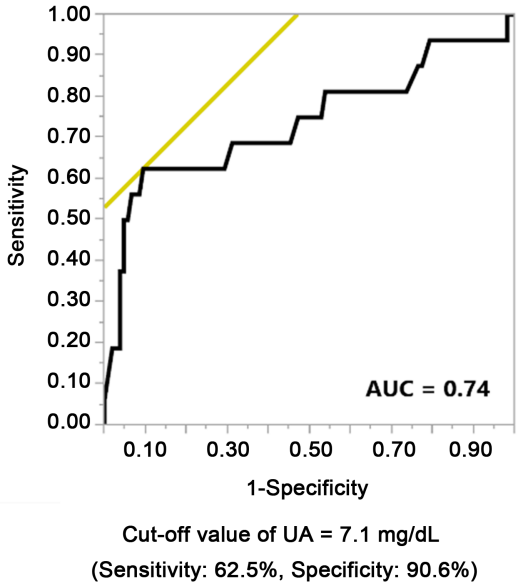


Figure 2. Receiver operating characteristic analysis to identify the optimal serum uric acid cut-off value for predicting an eGFR decline by ≥50% from baseline or end-stage renal disease during the follow-up examination period.

than in the non-HU group. The percentage of males (70.0% vs. 33.3%, $P = 0.002$) was significantly higher in the HU group than in the non-HU group.

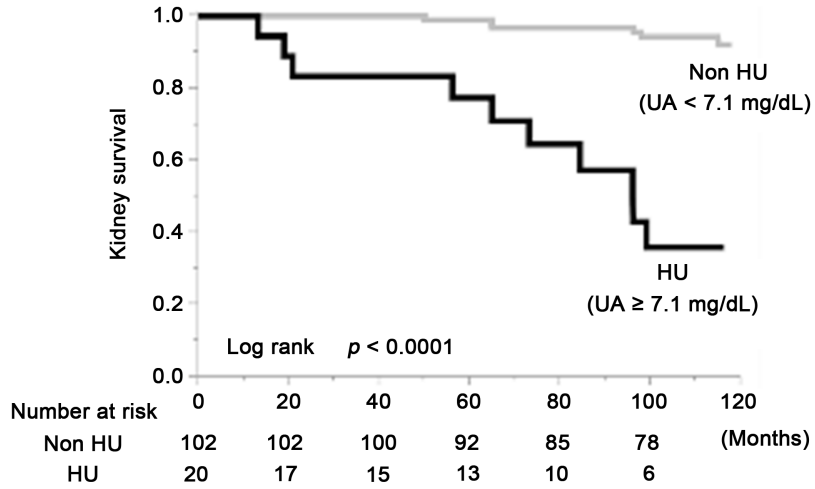
We performed a Kaplan-Meier analysis to assess kidney survival, with a ≥50% eGFR decline or ESRD used as the end-point. The kidney survival curves showed that the kidney survival rate of the CKD patients in the HU group was significantly lower than in the non-HU group (Figure 3(a)). At the 100-month follow-up examination, a decrease in eGFR value of at least a 50% was observed in 64.2% of the HU group (log rank, $P \leq 0.0001$). The results of the sex-stratified analyses showed a significantly lower kidney survival rate in the HU group than in the non-HU group (Figure 3(b) and Figure 3(c)).

3.4. HU as a Prognostic Indicator in CKD Patients

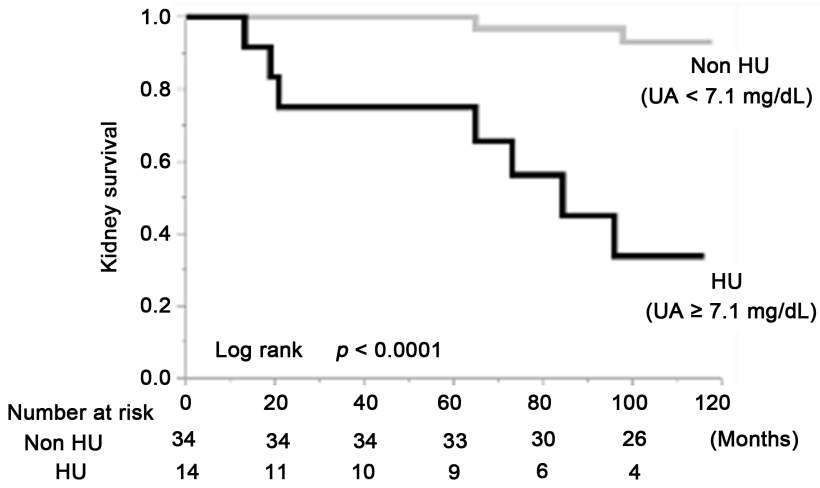
To determine whether severe HU (UA ≥ 7.1 mg/dL) was an independent predictor of a decline in renal function, we performed univariate and multivariate regression analyses based on the Cox hazard model for associations between the clinical findings and a ≥50% eGFR decline or ESRD during the follow-up period (Table 2). The results showed significant associations between HU [hazard ratio (HR) = 8.07, 95% CI (2.25 - 33.3), $P = 0.001$], diabetes mellitus (HR = 8.61, $P = 0.003$), and UACR (HR = 1.02, $P = 0.0005$) and a ≥50% eGFR decline or ESRD (Table 2(a)), and sex-stratified analysis yielded similar results. Both in male and female, HU, diabetes mellitus, UACR and eGFR were significantly associated with a ≥50% eGFR decline or ESRD (Table 2(b) and Table 2(c)).

3.5. Correlations between Serum UA Levels and Other Parameters

Since the serum UA values may have been affected by confounders, the baseline serum UA values were tested for correlations with clinical and laboratory para-



(a)



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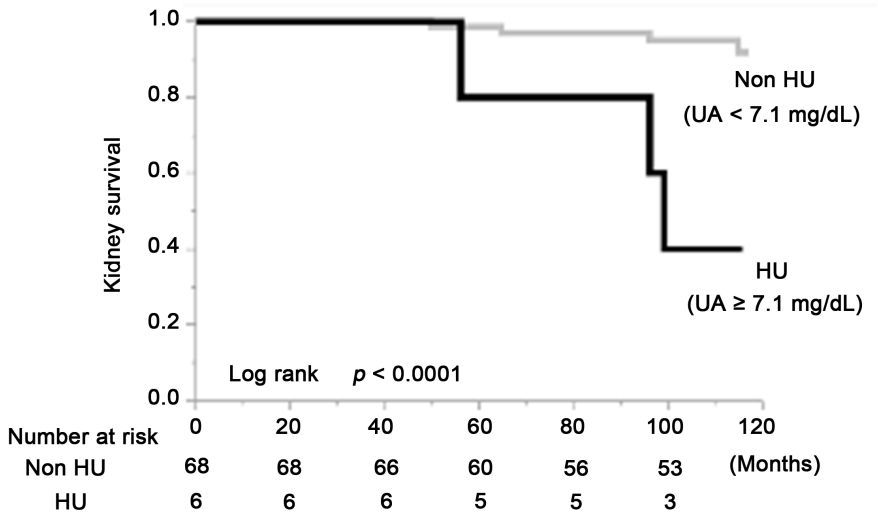


(c)

Figure 3. Kidney survival rate of the group with serum uric acid levels ≥7.1 mg/dL and group with serum uric acid levels <7.1 mg/dL in the total cohort (a); the males (b) and the females (c).

Table 2. Univariate and multivariate analysis of risk factors associated with a ≥50% eGFR decline or ESRD. (a) Total cohort n = 122; (b) male n = 48; (c) female n = 74.

(a)

Variables	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Age (1 year increase)	1.02 (0.98 - 1.06)	0.4	-	-
Male (vs. female)	2.25 (0.84 - 6.29)	0.1	-	-
Visceral fat area (10 cm^2 increase)	1.15 (1.07 - 1.23)	0.0001	1.01 (1.00 - 1.02)	0.3
Subcutaneous fat area (10 cm^2 increase)	1.04 (1.00 - 1.08)	0.04	1.00 (0.99 - 1.00)	0.1
IMT (1 mm increase)	1.72 (1.03 - 2.63)	0.04	0.93 (0.27 - 2.22)	0.9
eGFR (10 mL/min/1.73 m^2 increase)	0.52 (0.38 - 0.69)	<0.0001	0.63 (0.36 - 1.01)	0.1
Hemoglobin (1 g/dL increase)	0.69 (0.48 - 0.96)	0.03	1.45 (0.93 - 2.31)	0.1
Serum Albumin (1 g/dL increase)	0.27 (0.13 - 0.67)	0.001	0.33 (0.10 - 1.38)	0.1
UACR (10 mg/g creatinine increase)	1.02 (1.01 - 1.03)	<0.0001	1.02 (1.01 - 1.03)	0.0005
Hypertension (vs. no)	1.87 (0.65 - 6.70)	0.3	-	-
Hypercholesterolemia (vs. no)	1.40 (0.51 - 4.44)	0.5	-	-
Hypertriglyceridemia (vs. no)	1.22 (0.44 - 3.87)	0.7	-	-
Diabetes mellitus (vs. no)	5.93 (2.21 - 16.6)	0.0006	8.61 (2.11 - 40.4)	0.003
Hyperuricemia (UA ≥ 7.1 mg/dL) (vs. no)	14.27 (5.25 - 42.3)	<0.0001	8.07 (2.25 - 33.3)	0.001

(b)

Variables	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Age (1 year increase)	1.02 (0.97 - 1.08)	0.4	-	-
Visceral fat area (10 cm^2 increase)	1.12 (1.02 - 1.23)	0.02	1.00 (0.98 - 1.02)	0.6
Subcutaneous fat area (10 cm^2 increase)	1.04 (0.96 - 1.11)	0.2		
IMT(1 mm increase)	1.59 (0.87 - 2.68)	0.1	-	-
eGFR (10 mL/min/1.73 m^2 increase)	0.54 (0.37 - 0.77)	0.0008	0.39 (0.11 - 0.92)	0.03
Hemoglobin (1 g/dL increase)	0.58 (0.40 - 0.84)	0.003	3.03 (0.83 - 16.7)	0.1
Serum Albumin (1 g/dL increase)	0.31 (0.14 - 0.86)	0.009	0.10 (0.00 - 1.03)	0.1
UACR (10 mg/g creatinine increase)	1.02 (1.01 - 1.04)	0.0002	1.05 (1.01 - 1.10)	0.005
Hypertension (vs. no)	1.52 (0.37 - 10.2)	0.6	-	-
Hypercholesterolemia (vs. no)	2.96 (0.72 - 19.9)	0.2	-	-
Hypertriglyceridemia (vs. no)	1.64 (0.40 - 11.0)	0.5	-	-
Diabetes mellitus (vs. no)	2.98 (0.74 - 11.3)	0.1	37.9 (1.5 - 4579.1)	0.02
Hyperuricemia (UA ≥ 7.1 mg/dL) (vs. no)	10.84 (2.13 - 49.3)	0.002	24.6 (2.9 - 671.8)	0.002

(c)

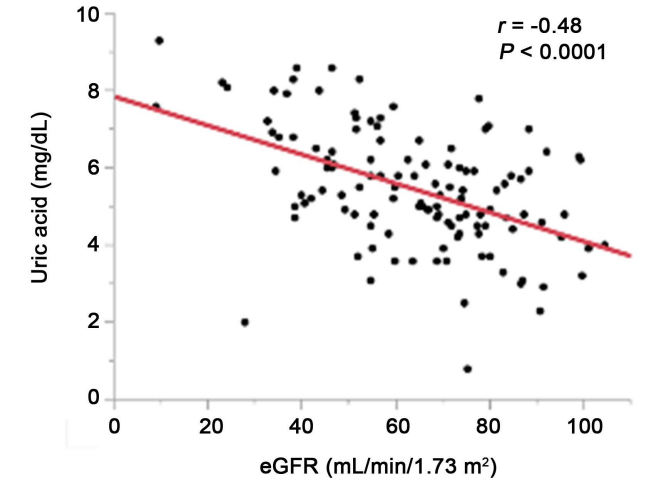
Variables	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Age (1 year increase)	1.01 (0.95 - 1.08)	0.7	-	-
Visceral fat area (10 cm^2 increase)	1.18 (1.04 - 1.34)	0.007	1.01 (0.98 - 1.03)	0.4
Subcutaneous fat area (10 cm^2 increase)	1.06 (1.01 - 1.11)	0.01	0.98 (0.96 - 0.99)	0.001
IMT (1 mm increase)	1.03 (0.12 - 3.42)	1.0	-	-
eGFR (10 mL/min/1.73 m^2 increase)	0.56 (0.33 - 0.87)	0.02	0.20 (0.03 - 0.74)	0.01
Hemoglobin (1 g/dL increase)	0.70 (0.37 - 1.34)	0.3	-	-
Serum Albumin (1 g/dL increase)	0.21 (0.01 - 3.40)	0.3	-	-
UACR (10 mg/g creatinine increase)	1.02 (1.01 - 1.03)	0.0004	1.02 (1.00 - 1.04)	0.1
Hypertension (vs. no)	1.88 (0.40 - 13.1)	0.5	-	-
Hypercholesterolemia (vs. no)	0.70 (0.15 - 3.55)	0.6	-	-
Hypertriglyceridemia (vs. no)	0.83 (0.18 - 4.20)	0.8	-	-
Diabetes mellitus (vs. no)	12.66 (2.72 - 88.5)	0.002	2062 (13 – 8,941,455)	0.0008
Hyperuricemia (UA ≥ 7.1 mg/dL) (vs. no)	15.88 (3.76 - 107.9)	0.0007	57.5 (2.8 - 31534.9)	0.007

Variables with P-values of less than 0.1 in the univariate model were included in the multivariate model. Abbreviation: ESRD, end-stage renal disease; n, number; CI = confidence interval; IMT, maximum cartoid intima-media thickness; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

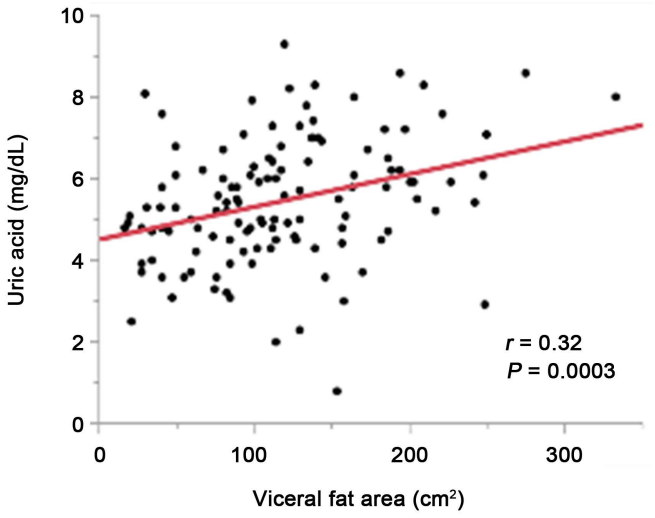
meters at baseline. As shown in Table 3, the UA levels were significantly negatively correlated with both eGFR (r = −0.48, P < 0.0001, Figure 4(a)) and HDL-C (r = −0.29, P = 0.001), and significantly positively correlated with SBP (r = 0.22, P = 0.01), DBP (r = 0.25, P = 0.006), MBP (r = 0.25, P = 0.007), TG (r = 0.29, P = 0.002), UACR (r = 0.25, P = 0.005), VFA (r = 0.32, P = 0.0003, Figure 4(b)), and IMT (r = 0.32, P = 0.0003, Figure 4(c)).

3.6. Comparison between the Clinical and Laboratory Findings in the Groups Established According to Serum UA Levels in the Propensity Score-Matched Cohorts

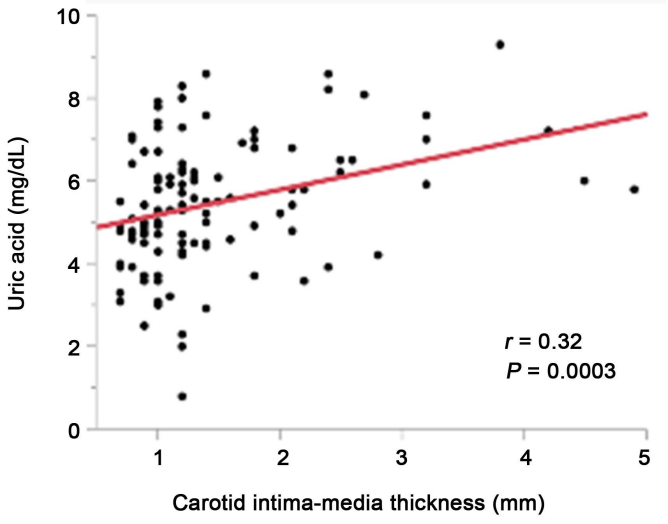
Since UA was correlated with gender, blood pressure, VFA, and especially with eGFR, we fit propensity score-matched models that included potential modifying variables (sex, eGFR, MBP, VFA) and performed subgroup analyses of the groups. We created a propensity score-matched cohort of HU patients and non-HU patients, and the comparisons between the clinical and laboratory findings of the two groups at baseline are summarized in Table 4. There were no significant differences between the propensity score-matched groups in any of the parameters except those associated with UA levels. The serum UA levels of the HU group (7.6 ± 0.4 mg/dL) were significantly higher than in the non-HU group (5.6 ± 1.5 mg/dL, P = 0.0003). The results of the Kaplan-Meier analysis with a ≥50% eGFR decline or ESRD as the end-point showed that the kidney survival rate of the HU group of CKD patients was significantly lower than in the non-HU group (Figure 5(a)). At the 100-month follow-up examination,



(a)

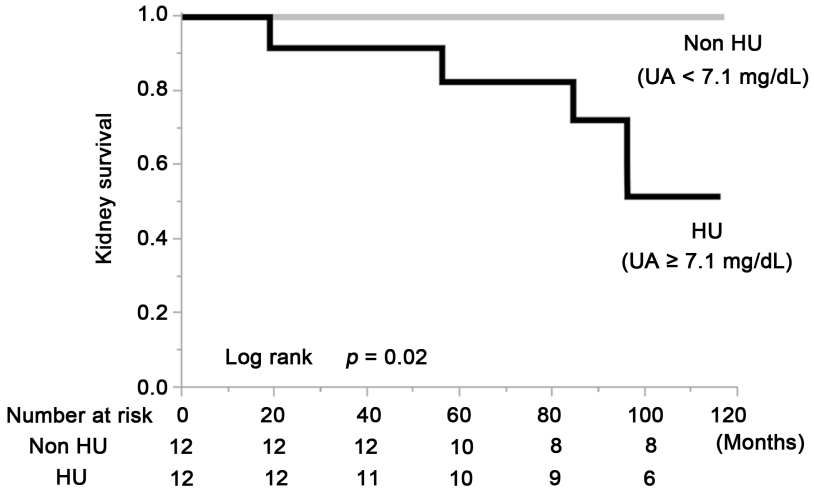


(b)

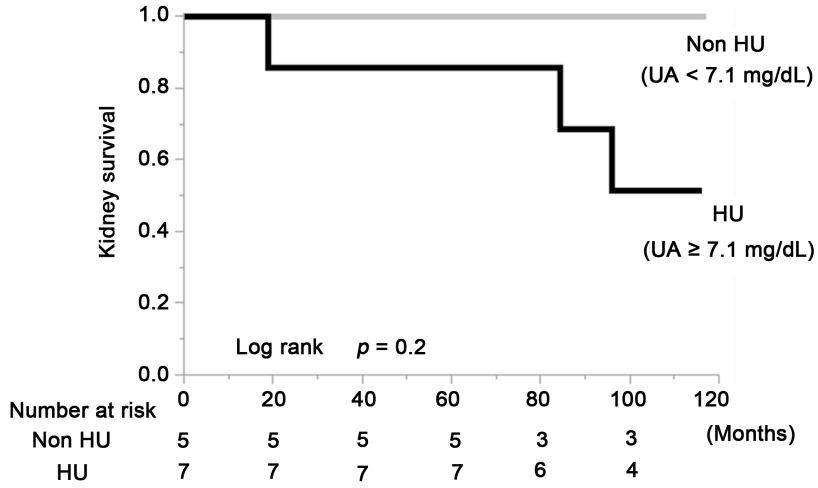


(c)

Figure 4. Relationship between serum uric acid levels and eGFR (a); visceral fat area (b), and maximum carotid intima-media thickness (c).



(a)



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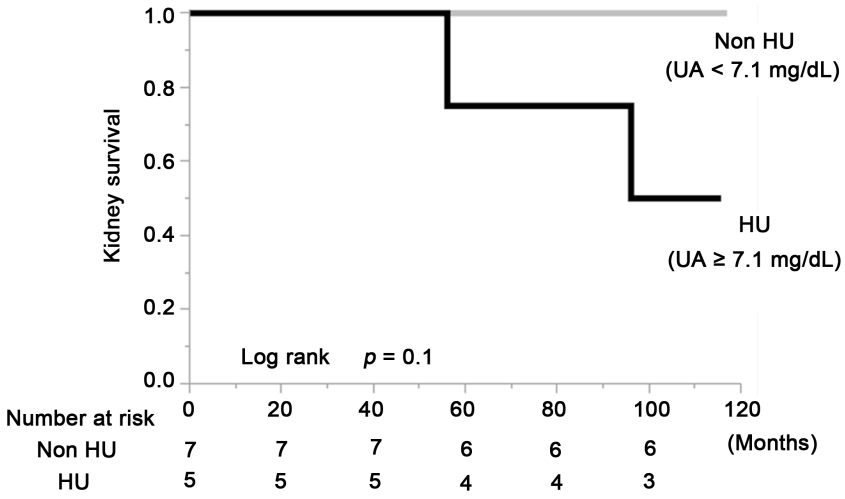

(c)

Figure 5. Kidney survival rate of the group with serum uric acid levels ≥7.1 mg/dL and group with serum uric acid levels <7.1 mg/dL in the total cohort (a); the males (b) and the females (c) of the propensity score-matched cohort.

Table 3. Coefficients of the correlation between serum uric acid levels and continuous variables.

Variables	Total n = 122		Male n = 48		Female n = 74	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
Clinical Findings						
Age (years)	0.05	0.6	0.05	0.7	0.04	0.7
SBP (mmHg)	0.22	0.01	0.29	0.048	0.07	0.6
DBP (mmHg)	0.25	0.006	0.28	0.1	0.11	0.4
MBP (mmHg)	0.25	0.007	0.30	0.04	0.09	0.4
BMI (kg/m^2)	0.17	0.1	0.11	0.5	0.15	0.2
Visceral fat area (cm^2)	0.32	0.0003	0.18	0.2	0.22	0.1
Subcutaneous fat area (cm^2)	0.09	0.3	0.20	0.2	0.27	0.02
IMT(mm)	0.32	0.0003	0.14	0.3	0.18	0.1
Laboratory Findings						
Serum Albumin (g/dL)	−0.14	0.1	−0.12	0.4	−0.09	0.8
Hemoglobin (g/dL)	0.05	0.6	−0.31	0.03	−0.04	0.4
eGFR (mL/min/1.73 m^2)	−0.48	< 0001	−0.47	0.0007	−0.48	<0.0001
Total Cholesterol (mg/dL)	0.05	0.6	−0.04	0.8	0.20	0.1
LDL Cholesterol (mg/dL)	0.08	0.4	−0.01	1.0	0.16	0.2
HDL Cholesterol (mg/dL)	−0.29	0.001	−0.35	0.01	−0.03	0.8
Triglyceride (mg/dL)	0.29	0.002	0.21	0.2	0.23	0.049
UACR (mg/g Cre)	0.25	0.005	0.26	0.1	0.11	0.4

Abbreviation: n, number; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index; IMT, maximum cartoid intima-media thickness; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

Table 4. Patient characteristics according to baseline serum uric acid levels. (Propensity score matched cohort n = 24).

Variables	Propensity score matched cohort			*P*-value	Standardized Differences
	Total	HU (UA ≥ 7.1 mg/dL)	Non HU (UA < 7.1 mg/dL)		
	n = 24	n = 12	n = 12		
Clinical Findings					
Age (years)	59.5 ± 16.1	55.8 ± 15.9	63.2 ± 16.0	0.3	0.464
Gender (Male; %)	50.0	58.3	41.7	0.4	0.337
SBP (mmHg)	127.1 ± 7.6	127.0 ± 7.3	127.1 ± 8.3	1.0	0.013
DBP (mmHg)	78.9 ± 5.4	79.3 ± 5.7	78.5 ± 5.2	0.7	0.147
MBP (mmHg)	94.9 ± 6.0	95.2 ± 6.2	94.7 ± 6.1	0.9	0.081
BMI (kg/m^2)	24.1 ± 3.6	23.4 ± 4.2	24.7 ± 3.0	0.4	0.356
Visceral fat area (cm^2)	139.4 ± 60.0	126.7 ± 60.8	152.2 ± 59.0	0.3	0.426
Subcutaneous fat area (cm^2)	179.9 ± 75.4	180.7 ± 97.8	179.0 ± 48.4	1.0	0.022
IMT(mm)	1.58 ± 1.05	1.46 ± 1.00	1.70 ± 1.14	0.6	0.224

Continued

Laboratory Findings					
Serum Albumin (g/dL)	4.1 ± 0.5	4.2 ± 0.4	4.0 ± 0.6	0.4	0.392
Hemoglobin (g/dL)	13.5 ± 1.7	13.4 ± 2.0	13.7 ± 1.5	0.7	0.170
eGFR (mL/min/1.73 m^2)	52.7 ± 15.8	52.9 ± 16.2	52.6 ± 16.1	1.0	0.019
Uric Acid (mg/dL)	6.6 ± 1.5	7.6 ± 0.4	5.6 ± 1.5	0.0003	1.822
Total Cholesterol (mg/dL)	221.8 ± 89.1	214.5 ± 55.7	229.0 ± 115.7	0.7	0.160
LDL Cholesterol (mg/dL)	136.6 ± 77.8	130.4 ± 41.3	142.7 ± 104.2	0.7	0.155
HDL Cholesterol (mg/dL)	51.6 ± 14.2	56.0 ± 16.7	47.2 ± 10.1	0.1	0.638
Triglyceride (mg/dL)	168.0 ± 84.0	140.4 ± 59.9	195.5 ± 97.4	0.1	0.681
UACR (mg/g Cre)	205.9 ± 373.1	263.5 ± 482.5	148.3 ± 225.9	0.5	0.306
Concomitant drugs					
Antihypertensive agents (%)	66.7	66.7	66.7	1.0	0.000
Antidyslipidemic agents (%)	29.2	25.0	33.3	0.7	0.183
Antidiabetic agents (%)	20.8	33.3	8.3	0.1	0.647
Corticosteroids (%)	20.8	25.0	16.7	0.6	0.205
Immunosuppressing agents (%)	12.5	8.3	16.7	0.9	0.256
Diuretics (%)	20.8	16.7	25.0	0.6	0.205
Comorbidities					
Hypertension (%)	70.8	66.7	75.0	0.7	0.183
HU (UA ≥ 7.1 mg/dL) (%)	50.0	100.0	0.0	<0.0001	-
Hypercholesterolemia (%)	41.7	41.7	41.7	1.0	0.000
Hypertriglyceridemia (%)	75.0	58.3	91.7	0.1	0.836
Diabetes mellitus (%)	25.0	33.3	16.7	0.3	0.391

Continuous values are expressed as means ± standard deviation. Count data are expressed as percentages. Abbreviation: n, number; HU, Hyperuricemia; UA, Uric Acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index; IMT, maximum cartoid intima-media thickness; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

there was a decrease in eGFR value at least a 50% or ESRD in 48.4% of the HU patients (log rank, $P = 0.02$). Although there were no statistically significant differences due to the limitation imposed by the small number of cases in the matched cohort, the sex-stratified analyses showed that the kidney survival rate of the CKD patients in the HU group was lower than in the non-HU group (**Figure 5(b)** and **Figure 5(c)**).

4. Discussion

The predictive value of UA in regard to the progression of CKD is matter of controversy [5]-[11]. Although a causal role of HU in CKD has not been established [23] [24], the results of several epidemiologic studies have indicated the existence of an association between HU and the development of CKD [25] [26]. HU has been found to independently predict the progression of kidney disease in nephrosclerosis [4], diabetic nephropathy [27] [28], IgA nephropathy [29]

[30] [31] [32], chronic allograft nephropathy [33], and CKD [10] [26], and HU has been reported to be associated with atherosclerosis [14] [34] and hypertension [35]. Thus, HU would seem to be associated with atherosclerosis and subsequent risk of hypertension and CKD, but the serum UA elevation in CKD patients makes it difficult to assess the pathophysiological role of UA in the progression of CKD. The present study focused on atherosclerosis/arteriosclerosis-related factors and examined the predictive value of HU in relation to CKD progression by using a propensity score-matching cohort.

The results of this study showed that even when eGFR was completely adjusted by propensity score matching (**Table 4**), the kidney survival rate of the HU group of CKD patients was significantly lower than in the non-HU group (**Figure 5(a)**, log rank, $P = 0.02$). Multivariate analysis of the Cox proportional hazards model showed that HU (UA ≥ 7.1 mg/dL) (HR= 8.07, $P = 0.001$) was significantly associated with a ≥50% eGFR decline or ESRD in the CKD patients (**Table 2(a)**). Since the BP of our cohort was well controlled (mean SBP/DBP = 125/76 mmHg) with antihypertensive agents (61.5%), hypertension was not a significant prognostic risk factor in this cohort. Rather, not only diabetes mellitus, HU was demonstrated to be a significant prognostic risk factor of CKD progression in this BP-controlled cohort. Women generally have lower UA levels, but it has never been clearly elucidated whether gender difference is involved in kidney disease progression [10] [26] [36] [37]. The results of our ROC analyses showed that the optimal UA cut-off value for discriminating ≥50% eGFR decline or ESRD in the total cohort was 7.1 mg/dL and because of the limitation of the small numbers of cases it was impossible to detect a gender difference at the cut-off value. However, our sex-stratified Kaplan-Meier survival curves and multivariate regression analyses based on the Cox hazard model showed similar significant associations between HU (UA ≥ 7.1 mg/dL) and a ≥50% eGFR decline or ESRD in both males and females (**Table 2**, **Figure 3**).

The results of the present study showed that UA was significantly correlated with VFA and with IMT (**Figure 4(b)** and **Figure 4(c)**). Recent experimental studies have indicated that UA may play a role in the pathogenesis of atherosclerosis and metabolic syndrome via the inflammatory pathway in adipose tissue [38] [39]. Several clinical studies have reported finding that a significant association between HU and VFA [40] [41] and that HU is a risk factor for carotid atherosclerosis [14]. Nakagawa *et al*. [42] reported finding evidence suggesting that HU might have a causal role in the development of obesity, metabolic syndrome, and endothelial dysfunction in rats fed a high-fructose, atherogenic [43], diet. The results of our study also indicate the existence of pathophysiological relationships between UA and VFA/IMT/CKD progression the same as in these other studies. We have to pay attention to the possibility that IMT and VFA are potential confounding factors or predictive markers for progression of kidney disease. The results of our multivariate analysis of the Cox proportional hazards model adjusted for eGFR, VFA and IMT indicated that HU was independently associated with a ≥50% eGFR decline or ESRD (**Table 2(a)**), and the propensity

score matched cohort, in which both VFA and IMT were higher in non-HU group (Table 4), showed that the kidney survival rate of the HU group of CKD patients was significantly lower than in the non-HU group (Figure 5(a)). These results indicate the most important finding that UA is an independent kidney outcome predictor. Although the mechanism of the effects of HU on atherosclerosis has not been fully elucidated, recent data have shown a direct harmful effect of UA on endothelial cells [42] [44] and smooth muscle cells [45] [46]. The precise mechanism of the nephrotoxicity of HU also remains unknown. However, HU has been found to induce systemic hypertension and afferent arteriolar sclerosis in animal models [47] [48], and high serum UA levels have been reported to be associated with renal arteriolosclerosis in humans [4] [49] [50]. These reports support the results of the present study.

The present study had several limitations. First, it was an observational study and had the typical limitations of a small number of subjects. Second, even if we used a propensity score-matched cohort as a control group, it is difficult to select a desirable control group.

5. Conclusion

The results obtained by using a propensity score-matched cohort in the present study showed that HU is an independent predictor of CKD progression. In addition to treatment of hypertension, treatment of HU in CKD patients will become more important.

Disclosure

All authors have no conflict of interest to disclose.

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PECS Block Provides Effective Postoperative Pain Management for Breast Cancer Surgery—A Retrospective Study

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Abstract

We investigated the efficacy of ultrasound-guided pectoral nerves (PECS) block for modified radical mastectomy surgery retrospectively. Methods: We measured that pain scores and the use of additional analgesic drugs were recorded in the postoperative care unit within 24 hours after the operation. Postoperative complications (*i.e.*, nausea and vomiting) were noted. Results: Patients who received the PECS block under general anesthesia (PECS group) reported lower visual analog scale pain scores at 0, 1, 2, 4, 6, 12, 24 hours after the operation than patients who did not receive PECS block under general anesthesia (control group). Moreover, the use of additional analgesic drugs during the first 24 hours after surgery was lower in the PECS group than in the control group. While in the postoperative care unit, the PECS group had less nausea and vomiting than the control group. Conclusion: The PECS block provides effective postoperative analgesia within the first 24 hours after breast cancer surgery.

Keywords

Pectoral Nerves Block, Postoperative Pain Management, Breast Cancer Surgery

1. Introduction

Acute postoperative pain following breast cancer surgery is often disregarded because the procedure is considered minimally invasive. However, if acute pain management is neglected, most patients will develop chronic post-mastectomy pain [1], which reduces quality of life.

To manage acute pain after breast cancer surgery, regional anesthesia is rec-

ommended [1] [2] as fentanyl is associated with a risk of vomiting and nausea. Therefore, to avoid the risk of postoperative nausea and vomiting, the injection of fentanyl is discouraged. Regional anesthesia such as thoracic epidural block (TEB) and thoracic paravertebral block (TPVB) can provide effective postoperative pain after breast cancer surgery [3] [4]. However, as the TEB and the TPVB are deep nerve blocks, we are hesitant to perform these techniques.

Pectoral nerves (PECS) block, previously described by Blanco *et al.* [5] [6], can anesthetize the intercostobrachial, lateral cutaneous branch, medial cutaneous nerve of the arm and forearm, and long thoracic and thoracodorsal nerves, which is analgesic at the lateral mammary area. Therefore, we hypothesized that the combination of general anesthesia and PECS block would provide effective analgesia for breast cancer surgery. However, there are a few reports of the efficacy of PECS block [7]. A research purpose in this study was to investigate about the efficacy of ultrasound-guided PECS block for breast cancer surgery.

2. Materials and Methods

Institutional review board approval was obtained (IRB number 14 - 167. February 2015), and we performed a retrospective examination of medical records of all patients who underwent for breast cancer surgery between April 1, 2014 and September 30, 2014. Perioperative data were collected, including age, height, weight, American Society of Anesthesiologists classification, operation time, anesthesia time, intraoperative fentanyl consumption, visual analog scale pain scores (at 0, 1, 2, 4, 6, 12, 24 hours postoperatively), additional analgesic drugs used, and the complications (*i.e.*, nausea and vomiting) within 24 hours after the operation. This study selected only breast cancer surgeries performed at the lateral site and modified radical mastectomy. In addition, we excluded some cases involving secondary surgery, bilateral breast cancers and performed regional anesthesia except the PECS block. Selected patients were divided into 2 groups. Patients in the PECS group received a PECS block after induction of anesthesia, whereas patients in the control group received no PECS block.

All surgeries were performed at Saitama Medical University International Medical Center. All PECS blocks were performed by the staff regional anesthesiologist. PECS block was conducted after the induction of anesthesia and was performed by administering 10 mL of 0.25% levobupivacaine between the pectorals major and pectorals minor at the third left rib and 20 mL of 0.25% levobupivacaine between the pectoralis minor and serratus muscles at the forth left rib by using a 50× high-frequency linear probe with the S-Nerve ultrasound system (SonoSite FUJIFILM, America) [4]. The analgesic drugs used in the perioperative period were remifentanil and fentanyl. Intravenous acetaminophen (1 g) or intravenous flurbiprofen (50 mg) was administered in all patients at the end of each operation. All patients were extubated in the operating room then transferred to the postanesthesia care unit (PACU).

In the PACU, patients were managed with a standard monitor, pain scores were measured by using a visual analog scale (VAS) at 0, 1, 2, 4, 6, 12, 24 hours

postoperatively by a nurse. If the patients reported operative wound pain, the lead physician ordered intravenous acetaminophen (1 g). If acetaminophen was ineffective, 15 mg intravenous pentazocine hydrochloride was started. A metoclopramide (10 mg) was injected to manage nausea and vomiting.

Postoperative pain scores (at 0, 1, 2, 4, 6, 12, 24 hours), the amount of acetaminophen used within 24 hours after operation, and the number of patients complained of nausea and vomiting within 24 after the operation were recorded.

Statistical analysis was performed utilizing JMP® 11 (SAS Institute Inc., Cary, NC, USA). Statistical tests included the Mann-Whitney's *U*-test and χ^2 test. Demographic data were expressed as mean (standard deviation, SD). Measurement data were expressed as mean (range). The level of significance for both tests was set at $P < 0.05$.

3. Results

During the study period, 254 patients (115 PECS and 139 controls) underwent breast cancer surgery; 8 patients in the PECS group and 17 patients in the control group were excluded because of some cases involving secondary surgery, bilateral breast cancers and performed regional anesthesia except the PECS block (Figure 1). Patients demographics and duration of surgery were comparable (Table 1). Fentanyl consumption was lower in the PECS group than in the control group. VAS scores were significantly lower in the PECS group than in the control group (Figure 2). The amount of additional acetaminophen (1 g) used was lower in the PECS group than in the control group ($P = 0.0012$) (Table 2). No patients required additional analgesic including the addition of intravenous pentazocine hydrochloride (15 mg).

Table 1. Demographic date.

Variable mean (SD)	PECS group (n = 107)	Control group (n = 122)	*P*
Age, y	57.36 (12.6)	57.09 (13.0)	0.98
Weight, kg	56.59 (10.1)	56.16 (9.4)	0.69
Height, cm	155 (6.6)	154 (5.6)	0.19
ASA class I, II, III, IV	49, 56, 2, 0	52, 66, 4, 0	
Duration of surgery, min	92 (38)	94 (32)	0.32
Duration of Anesthesia, min	130 (41)	132 (35)	0.49
Intraoperative fentanyl consumption, μg	280.37 (44.38)	304.91 (60.35)	0.0011

Table 2. Date within 24 after operation.

Variable	PECS group (n = 107)	Control group (n = 122)	*P*
Additional acetaminophen 1 g, number of dose	1.4 (0.6)	2.2 (0.8)	0.0012
Nausea and vomiting, number of patient	11	27	0.016

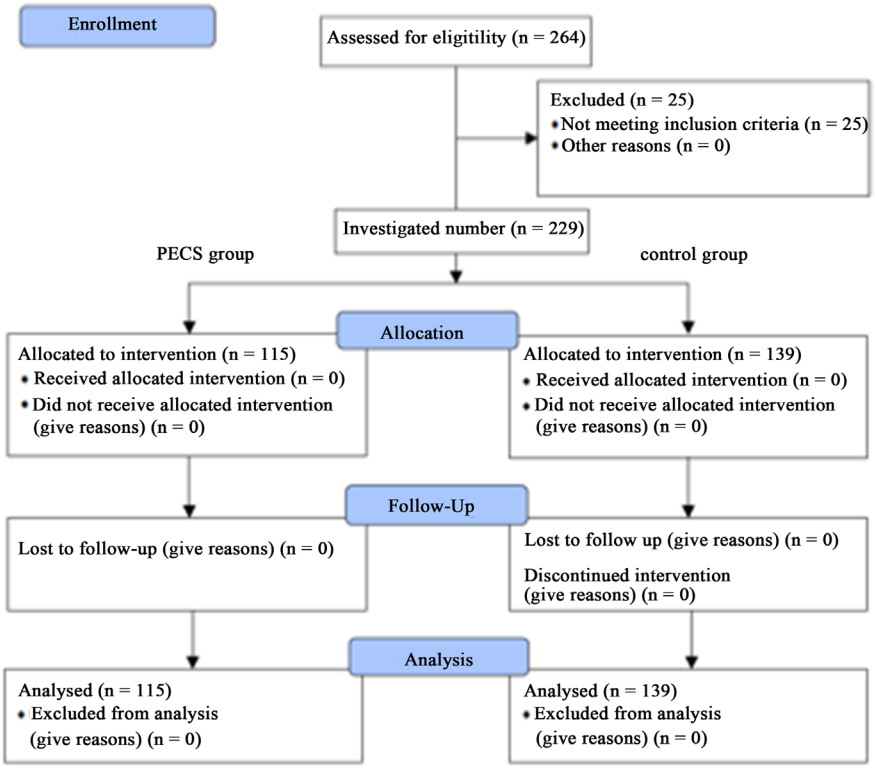

Figure 1. Flowchart of this study.

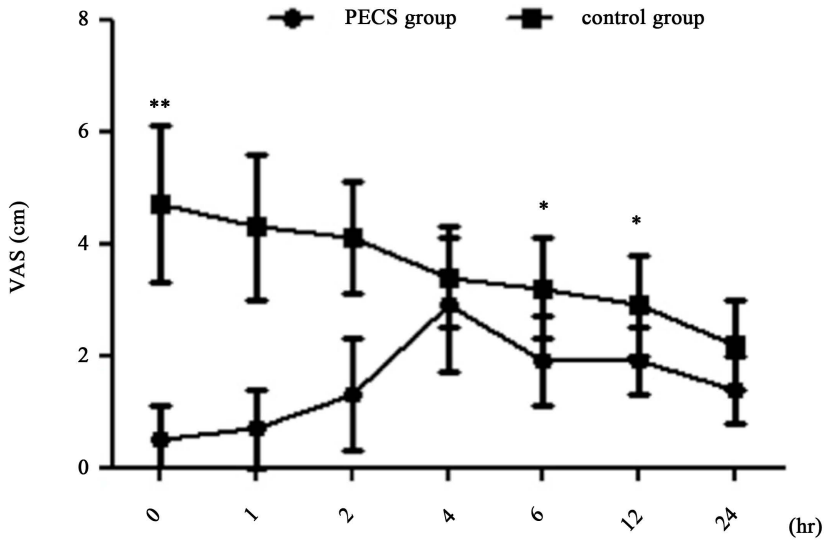

Figure 2. Postoperative VAS scores at 0, 1, 2, 4, 12, 24 hours postoperatively. *$P < 0.05$, **$P < 0.0001$.

4. Discussion

The VAS scores and the amount of additional acetaminophen (1 g) used within 24 after the operation were significantly lower in the PECS group than in the control group at all postoperative time periods. Compared with only general anesthesia alone, the combination of general anesthesia and regional anesthesia has the following benefit: 1) enhanced recovery after surgery, 2) reduction of

postoperative mortality and morbidity, 3) reduced incidence of surgical site infection, 4) reduced incidence of cancer recurrence [8] [9] [10] [11].

Both TEB and TPVB provide effective perioperative analgesia for breast cancer surgery. However, we have encountered some problems using both blocks. The TEB is performed using landmark technique, which is not always reliable, and there are also hemodynamic changes induced by sympathetic nervous system block. TPVB is a difficult block to perform because the injection site is deep. Therefore, it is not easy for us to perform these blocks. PECS block is easier in comparison because the injection point is shallower and the supine position is used, whereas the position in TEB and TPVB is lateral or prone.

A half-life of levobupivacaine is not thought to be over 12 hour. Therefore, the VAS score at 24 hours after the operation also showed me an importance of prevent analgesia. What we are saying is that decreasing the development of central sentitization attenuatess postoperative pain, decrease analgesic consumption, and enhances recovery [12].

This study has some limitations. The data were collected retrospectively and patients were not randomized. All PECS blocks were performed using the same methods (e.g., volume and concentration of levobupivacaine), but it is currently unclear whether these methods are correct. We chose the volume and concentration of local anesthetic according to an original regimen [6], but several studies have reported using different regimens [13] [14]. Before we assessed the quality of the block, we have inducted general anesthesia. Thus, we could not investigate the range of analgesic. We also want to investigate the incidence of postoperative chronic pain. However we cannot get in touch with all patients. PECS block cannot anesthetize the internal mammary area. We manage this problem by performing a transversus thoracic muscle plane block (TTP) block [15], which anesthetizes the internal mammary are via injection of a local anesthetic in the TTP. In the future, some standardized prospective randomized trials are needed to investigate these various issues.

5. Conclusions

The PECS block showed lower visual analog scale pain scores at 0, 1, 2, 4, 6, 12, 24 hours after the operation. Moreover, the PECS block was lower the number of additional analgesic drugs during the first 24 hours after surgery.

We recommend PECS block for modified radical mastectomy surgery.

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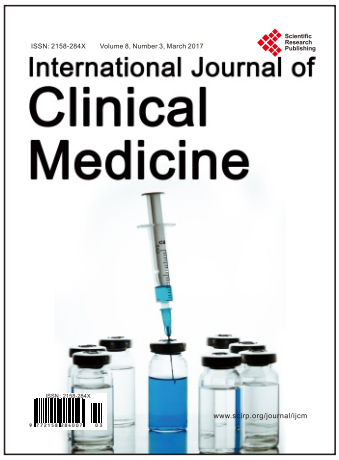

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