Title: Raynaud's Disease and Clinical Challenges: a Minireview of Literature with a Spotlight on Acupuncture

Running Title: Raynaud's Disease and Acupuncture

ABSTRACT

Background: Primary Raynaud's disease preferentially afflicts women with 5% prevalence rate reported in general population, manifests triphasic color phenomenon along with paresthesia involving distal digits and toes and triggered by severe cold and stress. **Objective:**This review critically describes several perspectives of Raynaud's diseases with a focus on medical acupuncture. **Methods:** Electronic searches of relevant data prior to 2019 published in PubMed, MEDLINE, Google Scholar, and ScienceDirect databases were made using the Boolean operators and keywords. Finally, 32 articles that addressed specifically Raynaud's disease and acupuncture were retained for this minireview.**Results:** Raynaud's disease classified into primary and secondary is poorly understood phenomenon, lacks standard care and, hence,needs patient-centered holistic approach. Evidently, medical acupuncture with safe clinical profile has been effectively used as an alternative therapy in Raynaud's disease. Outcome results with the use of conservative approaches, modern therapies, behavioral interventions and medical acupuncture vary considerably across the board and primary RD carries better prognosis than secondary RD. **Conclusion:** Both Raynaud's disease phenomena are complex conditions; need individualized treatment approach including surgical in refractory cases and further rigor studies to unravel their pathophysiology pathways and standardized interventions.

Keywords; Raynaud's disease, medical acupuncture, tricolor phenomenon, vasospastic attacks, integrative treatment

Introduction

Primary Raynaud's disease

Raynaud's disease (RD) first described by Maurice Raynaud as "a local asphyxia of extremities" in 1862is an idiopathic disorder with no underlying pathologies and precipitated by cold or severe emotional upset. RD is characterized by mild to severe intermittent vasospastic episodes of arteries of acral distal digits and toes, rarely nose and ears. RD is accompanied by extremity paresthesia, which is due to sensory nerve ischemia [1,2]. Vasospastic attacks lead to ischemic blanching (pallor to whitening) of all fingers,followed by cyanosisdue to desaturation of residual blood (blue)and finally reperfusion hyperemia (red)[1-5]. The trio of white or pale, blue and red color is termed as tricolor phenomenon of RD. RD is typically seen in a woman of age 20 to 30 years, affects females twice compared to their counterparts, and its prevalence is up to 5% in general population which varies geographically around the world [4]. The diagnostic criteria for primary RD include typical symmetrical symptoms of digital vasospasm, absence of peripheral vascular obstructive disease and tissue necrosis or digital ulceration or gangrene, normal nailfold capillaries, and a negative antinuclear antibody test and normal sedimentation rate. The diagnostic criteria and laboratory workup tend to rule out most systemic, autoimmune and mixed or deep connective tissue conditions underlying secondary Raynaud's phenomenon [1-6]. Primary RD is a diagnosis of exclusion and reversible condition.

Secondary Raynaud's phenomenon

Conversely, secondary Raynaud's disease (SRD) is caused primarily by several underlying genetic and autoimmune connective tissue diseases such as Marfan's syndrome, systemic sclerosis or scleroderma, systemic lupus erythromatosis, rheumatoid arthritis, Sjögren's syndrome and mixed connective tissue disease, hypothyroidism, hematologic disease, anticancer drugs and other diseases [1,6]. SRD tends to occur after the age of 30, co-occurs with multiple systemic diseases and manifests additional asymmetrical, severe pain, specific autoantibodies, and ulcerations on distal digits and toes due to ischemia. Furthermore, microvascular disease of nail capillaries concerning SRD leads to several complications including disability and amputations [1,5,7].However, both primary and secondary Raynaud's

phenomenon share some clinical and diagnostic features and the prevalence of secondary RP is much higher (up 90%) among patients with comorbid systemic conditions. This minireview appraises critically the phenomenon of Raynaud's disease and its management with special focus on medical acupuncture. The significance of this narrative review lies in the fact that there is a scanty published literature on RD in Saudi Arabia.

Methods

Search Strategy

The relevant literature published in English prior to 2019 was searched in PubMed, Google Scholar, and ScienceDirect databases. The Boolean operators and keywords used in multiple e-searches were "Raynaud's disease AND medical Acupuncture OR laboratory investigations OR imaging procedures AND treatment interventions AND medical acupuncture AND action mechanism. The search strategy and the keywords were modified as appropriate according to the searched database. In addition, references included in full text articles that focused mainly on details of Raynaud's phenomena and medical acupuncture were reviewed for inclusion in this critical review.

Search Results

Hundreds of thousands articles concerning medical acupuncture and Raynaud's disease were retrieved and reviewed by three independent researchers. Our focus was on full articles describing RP,its management and medical acupuncture. In addition, we also briefly reviewed articles that highlighted doses, and adverse effects of various integrative therapies used in RD and SRD. These articles were reviewed critically and the brief sketches of important contents were incorporated in this narrative review. The additional inclusion criteria were free access to full articles, papers containing salient socioclinical features and treatment interventions of RD and SRD. All types of related studies such as systematic reviews, meta-analyses, randomized clinical trials, observational studies, case series and single case reports were included for reviewing. Screening of retrieved records excluded more than two thousand papers. More than nine hundred records were reviewed for eligibility purpose. After removing

duplications, unrelated articles, articles cited in systematic reviews and meta-analysis, full articles not accessible, and irrelevant information, 56 articles were left for further review. Finally, three reviewers agreed to include 32 published studies (Figure. 1).

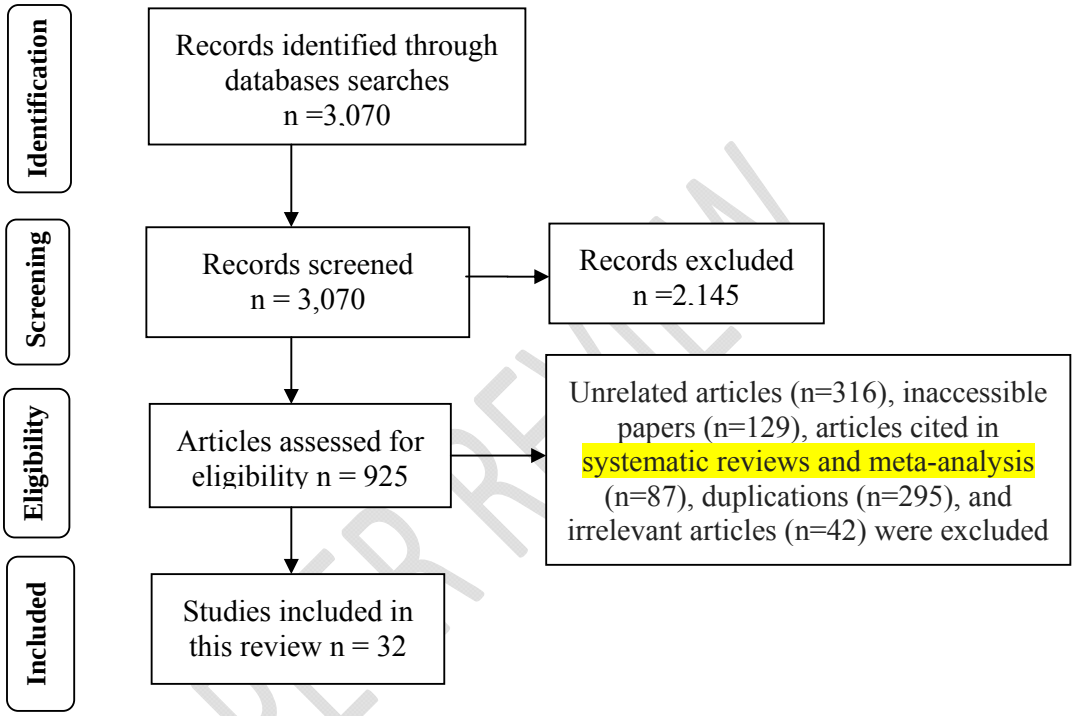


Figure 1 Prisma diagram summarizing the flow of search results

Results

Pathophysiology

Despite considerable research, the pathophysiology of primary RD is yet to be understood and, therefore, most researchers proposed it to be functional, idiopathic disease (RD) while SRD is multifactorial in nature [1-4]. However, several vascular, intravascular, neural and biochemical mechanisms regulating the cutaneous vascular tone, i.e., imbalance of vasodilatation and vasoconstriction have been identified in RD phenomenon. Current studies focus on the interactions and cascades of the endothelium with calcitonin gene-related peptide (CGRP), neuropeptide Y, nitric oxide, serotonin, thromboxane, angiotensin and endothelin-1 [1-3,6,]. Thus,

temporary vasospasm in RD and fixed digital artery obstruction involving neural network in SRD are other mechanical means to explain both phenomena [1,8]. Furthermore, alterations in peripheral postsynaptic adrenoceptors (mainly alpha-$_{2C}$AR) activity has been implicated, specifically either their overexpression or hyperactivity leading to enhanced smooth muscle constriction [1,8]. In addition, hyperactive sympathetic nervous system especially the alpha-1 receptor located on vascular smooth muscle linked with increase in norepinephrine release, and accordingly contributes to the constriction of smooth muscles underlying RD. This action is competitively inhibited by alpha 1-selective blockers (Prazosin) both in RD and SRD. About 66% of patients with RD improves with the use of Prazosin; reduction in frequency and duration of vasospastic attacks and flow of blood in distal fingers and toes [1,8]. Initially patients given Prazosin may develop postural hypotension; however, patients tend to develop tolerance to this effect. Of note, the presynaptic alpha 2 receptor located on the nerve terminals remains intact, preventing tachycardia seen with non-selective alpha blockers [8]. The key factors influencing these pathophysiological mechanisms are endothelin-1 and endothelial dysfunction linked with decreased nitric oxide (NO) synthesis resulting in imbalance of vasoconstriction and vasodilatation [1,2,6-8]. Hence, phosphodiesterase V (PDE-V) inhibitors impact vascular effects of endothelin-1, improve endothelial function, and enhance NO-related effects are considered the most promising agents for future treatment and research,especially in SRD[2].For further details of pathophysiological alterations underpinning both RD and SRD and mechanisms of action and effects of various conventional medications, see these sources[2,6,8].Among vascular mediators, nitric oxide, endothelin-1, serotonin, thromboxane, and angiotensin reported to play major role in the pathogenesis of RD. Neural mediators including calcitonin gene-related peptide and neuropeptide Y, and agents interacting with α-$_{2C}$adrenoceptors have also been implicated in the impairment of vasodilatation and vasoconstriction equation. In addition, platelet activation, fibrinolysis, and oxidative stress may also contribute to the pathophysiology of RD [9-11].Overall, pathophysiological vascular conditions complicated by structural abnormalities concerning endothelium and neural system are suggested to play the major role in the pathophysiology of Raynaud's phenomenon (both RD and SRD).

Diagnosis and Prognosis

The diagnosis of RD is classically based on comprehensive history given by patients concerning a series of tricolor phases in distal digits and toes induced by stress or cold. Further support may come from photos taken by the patient as vasospastic episodes are rarely observed in the clinical setting [8].Upper extremity pulse volume recording is oftenperformed to rule out proximal arterial obstruction found in secondary RD. Furthermore, digitalpressure and photoplethysmographic waveforms are usedto differentiate between patients with underlying vasospastic (RD) and obstructive pathology (SRD), the latter condition is characterized by decreased pressures and blunted waveforms. Laser Doppler and digital thermography could give differentiating clues between two Raynaud's phenomena. Cold challenge testing, such as, ice water immersionwith temperature recovery is highly sensitive but lacks specificity [3,6,8]. In addition, serologic screening, i.e., antinuclear antibody and rheumatoid factor and advanced imaging might exclude associated mix connective tissue disorders and autoimmune disorders underpinning SRD.The triphasiccolor phenomenon, i.e., well-demarcated pallor with one other phase of cyanosis (blue) or rubor (red) certainly helps in making the diagnosis of RD [3]. The differential diagnoses of primary and secondary Raynaud's phenomenon include the following conditions; scleroderma, systemic lupus erythematosus, dermatomyositis, Sjögren's syndrome, undifferentiated connective-tissuedisease, mixed connective-tissue disease, cryoglobulins, cryofibrinogens, paraneoplastic disorder, cold agglutinin, hypothyroidism, obstructivedisease, carpaltunnel syndrome, vibration exposure,frostbite, sympathomimetic disorder, interferon alfa-2b, ergotamine and chemotherapeutic drugs [6].

The prognosis of patients with RD is relatively better than their counterparts with SRD. Patients with SRD tend to die earlier due to its complications including pulmonary hypertension, cardiac diseases, chronic disability, amputations and other injuries [8]. In a nutshell, a comprehensive history, relevant laboratory investigations and imaging methods need to be used as diagnostic tools for primary and secondary Raynaud's phenomenon.

Patient-centered Treatment Perspective

Individual patient-centered approach is advisable because of ill-understood pathophysiology of primary and secondary Raynaud's disease. In patients with RD, lifestyle modifications are better choices than conventional medications. Avoidance of cold exposure, keeping body warm, quitting of smoking, minimizing stressors through stress management and discontinuing estrogen and chemotherapeutic agents are conservative methods, which are invariably effective among patients with RD.In case, patient with RD does not respond to aforesaid approaches due to chronicity, unaffected frequency and duration of vasospastic attacks, and intense severity of symptoms may require additional medical treatment by means of topical nitroglycerin or low-dosesof calcium channel blockers (CCBs) [1,2,10].

Evidently, the use of complementary and integrative medicine is rising globally attributed to multiple factors including cost-effectiveness and safe clinical profile. The therapies effective in RD may include but not limited to meditation, biofeedback, mindfulness behavior therapy, exercise and stretching, cupping (Hijamah), sleep hygiene,essential fatty acids, l-arginine, glucosaminoglycans, N-Acetylcysteine, acupuncture, moxibustion, and Ginkgo biloba (Seredrine) and Chinese herbs [3,8,12,13].

Patients with SRD need conventional interventionsincluding endothelin-1 receptor blocker (Bosentan) and immunosuppressant drugs for comorbid autoimmune diseases [1,8,14]. Simultaneously, the patients with SRD also require treatment for resolving manifestations of RD because identifying which of the two syndromes developed first often posits multiple diagnostic and treatment challenges to professional practitioners. Notably, treatments directed towards SRD do not improve RD phenomenon [8].Currently, a variety of conventional medications with moderate therapeutic effects (about 35% to 50% reduction in severity, duration and frequency of vasospasm) are prescribed to patients with RD or SRD and these include CCBs (dihydropyridine vasodilators- nifedipine,10-30mg od-tid and nondihydropyridine- Diltiazem,30-120 tid) and PDE-V inhibitors increase cGMP by decreasing its degradation in vascular smooth muscle cells and dilates micro-and macro-vascular system); tab Sildenafil,

50mg od-bid, tab Tadalafil, 20mg alternate day, tab Verdenafil 10mg bid). Angiotensin-converting enzyme (ACE I - a constrictor of smooth muscles) inhibitors (Captopril,12.5-25 mg orally bid-tid increases digital blood flow and Enalopril, 20 mg orally/day with mixed results and ACE II inhibitors such as Losartan, 12.5-50 mg/day orally) are reported to cause 50% reduction in severity and attack frequency. Oral (linked with dizziness and headache) or topical nitrates, i.e.,nitroglycerin,0.5 gm gel qid is effective in severe RD and SRP. Like prostacyclins/prostaglandins analogue, such as,Iloprost (a stable analog of Epoprostenol-prostaglandin I2,0.5-2 ng/kg/min IV or 50 microgm orally bid), Epoprostenol (a natural prostaglandin with vasodilator and antiplatelet actions)1-2 ng/kg/min, given IV to patients with RD tends to increase both digital blood flow and temperature but the improvement remained short-lasting. Other medicationsα-1adrenoceptors blockers such as Prazosin, 1mg tid orally, and endothelin-1 blocker, i.e., Bosentan, 62.5 mg bidorallydecrease the incidence of new ulcers in scleroderma through the action of vasodilatation.The selective serotonin reuptake inhibitors, such as Fluoxetine, 20-40mg/day orally relieve symptoms of RDalso through causing vasodilatation. Protein tyrosine kinase inhibitors (PTK) mediate the activity of PTK Pathwaysinfluenced by impaired endothelium-dependent vasodilatation. Secondly, PTK inhibitorsreduce neuropeptides Y which is a strong vasoconstrictor and produce good results in RD. Rho-kinase inhibitors, such as, Fasudil, 40-80mg have no significant effect on RD; however, with higher doses positive effect may be possible and, hence, needs further studies. Statin(Atorvastatin, 40mg) is reported to impact endothelial markersactivation in RP comorbid with systemic sclerosis, which areIL-6, TNF-alpha, ET-1, nitric oxide, thrombomodulin, soluble E-selectin, von Willebrand factor, monocyte chemoattractant, fibrinogen, high sensitivity C-reactive protein, erythrocyte sedimentation rate, lipid peroxide, and malonylaldehyde [1-5,7,8,11,12,14-18]. Allaforesaid conventional medications are reported to invariably improve RDand SRD but are associated with headache, nausea, dizziness or light-headedness, excessive tiredness, flushing,tachycardia, ankle edema and hypotension. Overall,peripheral vasodilators especially CCBs and PDE-5 inhibitors are most effective in RD and obstructed digital arteries in RD, respectively [1,5,8].Patients with RD are reported to have low blood pressure and the use of nifedipine or other CCBs may aggravate hypotension [1,5,6,8] and, therefore, caution should be used in using these medications among patients susceptible to develop hypotension.

Surgical Interventions

Anesthetists and surgeons have special role in the management of patients with SRD associated with several complications such as chronic nonhealing ulcers, disability, amputations and gangrene. In initial stage, local debridement of dead tissue or removal of the fingernail is effective in digital ulcer; however, 10% to 20% of patients require partial or complete phalangectomy [8]. For patients with nonhealing ulcerations, the use of PDE5 inhibitors along with central or digital sympathectomy has shown good results both in RD and SRD [5,8,11]. Invasive and noninvasive therapies withbetter efficacyin ulcer healing and pain reduction used in RD include botulinum toxin [19], sympathetic block [20], thoracoscopic sympathectomy [21], digitalsympathectomy [22], adventitial stripping of hand and digital arteries [22,23], transcutaneous nerve stimulation [24],fat grafting [25] and spinal cord stimulators [26].Botulinum toxinA (chemical sympathectomy), its interdigital injections, is reported to reduce pain and numbness along with frequency of vasospastic attacks, and enhance healing of digital ulcers and blood flow in patients with Raynaud's phenomenon. Botulinum toxinimpacts inhibition of vasospasm by blocking cold-induced vasoconstriction and by preventing recruitment of alpha-2 receptors to vascular smooth muscle in cold conditions [19]. Overall, none of these therapies including conservative, complementary and alternative medicine (CAM), and conventional medications are considered standard of care in Raynaud' phenomenon and, hence, patient-centered approach needs to be pursued in the management of Raynaud's disease. Comprehensive details of conventional, CAM and surgical therapies in both RD/SRD are available here [1-8].

Medical Acupuncture

Standard Acupoints

Evidently, there are many acupuncture points used in Raynaud's disease especially secondary RP [27,28]. However, these acupuncture points and many others are frequently used in RD phenomenon associated with autoimmune systemic diseases, such as, systemic sclerosis, lupus, rheumatoid arthritis, and connective tissue diseases: LU5, LU9, ST36, ST40, ST41, SP1, SP6, SP9, SI3, UB15, Liv3, Ren12, Ren14, LI4, SP3, LR2, LR3, KI3, KI6, PC7, TE4, TE5, BL15, BL20, BL23, GB24, GB30, GB39,

BL38,CV14, CV12, CV13, SP1, SP6, SP9, LE10, PC6, HT1, C3-C7, L1-L4, LI11, LI13, UE9, and LR3, LR5. Furthermore, LI4 and SI3 acupuncture points are preferentially used in idiopathic RD.

Acupuncture Needles

Disposable stainless needles,with a diameter of 0.16 mm and length of 40mm, sterilized with ethylene oxide gasare commonly used by acupuncturists. The needles are inserted0.5–0.7 cm deep depending on the part ofthe body for achieving de qi phenomenon perceived as heaviness and numbness with manual stimulation or electrostimulation. Subsequently, needles are retained for 5 to 10 minutes without further stimulation. Patients with SRD need usually two courses of 16 sessions twice weekly in order to achieve satisfactory outcome within two months.

Mechanism of acupuncture

An understanding of underlying mechanisms of RD and SR phenomenon provides multiple windows for identifying working methods of various interventions including acupuncture. Concerningtherapeutic effects of acupuncture on primary RP, two mechanisms could be postulated: a reduction of the sympathetic tone and the release of vasoactive mediators, especially calcitonin gene-related peptides. An increased sympathetic activity plays an important role in eliciting vasospastic attacks in primary RP. Medical acupuncture, a holistic treatment helps in reducing the sympathetic tone and, hence, improves symptoms of RP through vasodilatory effect. Furthermore, acupuncture releases substance P and CGRP from peripheral terminals of primary sensory neurons, the latterbeing one of the most potent vasodilators [1-4,6.8,12,27]. Adeficiency of CGRP is reported in patients withprimary RD and evidently, the effect of acupuncture on ischaemia is more similar to CGRP than to a reduction of the sympathetic tone [1-4,12]. Acupuncture therapy does not impactthe meanduration and the severity of attacks which might be due to elevation of the threshold for eliciting avasospastic attack. Coffman et al. have also reported aforesaid findings in patients managed with vasoactive drugs [29]. Ketanserin (given 40mg orally) is a 5-HT_2 receptor antagonist along with weak alpha 1-adrenoceptor antagonistic action and inhibits the vasoconstriction produced by serotonin. Ketanserin not approved by FDA is used in patients with hypertension and RP, and tends to decrease frequency of vasospastic attacks and subjective improvement in various symptoms of both

idiopathic RD and SRD [30,31]. Ketanserin is associated with prolongation of QT interval, arrhythmia and syncope and, hence, needs to be used carefully among susceptible patients receiving diuretics causing depletion of potassium, or on antiarrhythmic drugs. Similarly, precaution should be exercised in using Ketanserin in patients with pathological bradycardia, hypokalemia, heart block of second and third degree, ventricular arrhythmia, and QT prolongation [29,31].

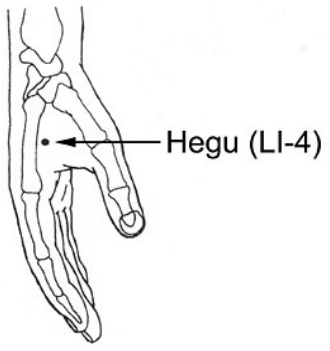
The vasomotor activity of acupuncture is identified using indocyanine green (ICG) perfusion. This method provides useful information about vascular perfusion as well as functional integrity of peripheral vasculature [32,33]. Overall, several mechanical actions and therapeutic effects of acupuncture among patients with Raynaud's syndrome can be elucidated by various methods including ICG [12,32,33].

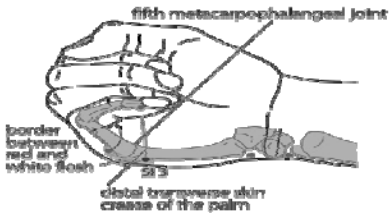
In conclusion, traditional Chinese acupuncture tends to reduce frequency of vasospastic attacks with its severity and paresthesia in primary RD but the effects may not be long-lasting. Therefore, acupuncture needs to be done minimum for two months. Evidently, the effectiveness of medical acupuncture with better safe clinical profile is comparable to that described for CCBs especially nifedipine which is associated with adverse effects [4]. We illustrate the efficacy of medical acupuncture in Raynaud's phenomenon by two clinical cases seen in different settings, in addition to third case treated with partial improvement by a number of treatments but finally responded successfully to rituximab.

.Clinical Vignette

A 32-year-old women was diagnosed with Raynaud's disease of short duration based on comprehensive history of bilateral tricolor phenomenon, i.e., blenching (yellow to white color), cyanosis (blue), and hyperemia (red color) of distal digits and toes triggered by psychological stress in terms of violent arguments with her husband and severe cold. The diagnosis of primary RD was further supported by negative physical examination including no ulcers on digits or toes. Systemic evaluation found no physical or psychiatric diseases including autoimmune disorders and deep connective tissue diseases. Basic and advanced laboratory investigations were within normal limits. Patient reported no history of diabetes mellitus, hypertension, obesity or metabolic syndrome, musculoskeletal disorders, scleroderma, systemic lupus erythematosus and peripheral arterial occlusive diseases. She did not use any treatment including ointments or analgesics because the intensity of symptoms including pain was bearable. She read the relevant literature on Google.com regarding

the management of RD and the only treatment found without side effects was medical acupuncture. Therefore, she opted for medical acupuncture therapy. The patient was explained the procedure of acupuncture including needles and safety issues and, thereafter, she voluntarily gave oral consent. Literature suggests that Hegu (LI4) and Houxi (SI3) are the two most frequently used acupuncture points in functional Raynaud's phenomenon (see Figure 2&3) [33]. Acupoint sites were sterilized with ethanol, and aseptic stainless needles (0.25 × 40 mm) were inserted 1.5-2.0 cm and manipulated for 10 seconds until de qi sensation (numbness and heaviness) was achieved; the needles then remained untouched. After 10 minutes, the needles were taken out without manipulation. This technique was repeated twice weekly for six weeks; 12 sessions, each one for 10-5 minutes based on improvement. The patient showed complete recovery concerning pain severity, joint stiffness and the tricolor of her fingers and toes. On visual analogue scale of 0-10 points, she also reported improvement in all symptoms by indicating point 0-1 that means nearly complete recovery. This case described in details substantiates the results of acupuncture therapy in an African-American patient with Raynaud's phenomenon [34]. Accordingly, acupuncture with anti-inflammatory effect is relatively safe and should be considered as an alternative treatment for vasospastic episodes and pain associated with RP. The third case of 55-year old Saudi female with chronic refractory PRD was treated unsuccessfully with many drugs but she finally responded to rituximab, a drug used in many autoimmune diseases and cancers [35].





SI3

Figure.2.Hegu LI4-between metacarpal I and II [36]: Figure 3. SI3 [37]

Summary

Primary Raynaud's disease is an idiopathic disease triggered by severe cold and overwhelming stress and is a diagnosis of exclusion. Raynaud's disease is characterized by tricolor phenomenon of distal digits and toes along with paresthesia and despite extensive research its pathophysiology is poorly understood. Secondary Raynaud's disease is a multifactorial disorder, co-occurs with various systemic diseases and shares a number of clinical features with RD. A battery of investigations and advanced imaging techniques are needed to diagnose the underlying conditions of secondary RD. A variety of conservative and complementary and alternative medicines and integrative therapies are reported to have variable efficacy in primary and secondary Raynaud's phenomenon. However, conventional medications especially CCBs such as nifedipine, phosphodiesterase V inhibitors (PDEV) and endothelin-1 inhibitors and others are also used effectively in patients with RP but most of them have potential adverse effects. Therefore, most patients with RP opt for complementary and alternative therapies not associated with adverse effects and at the same time cost-effective in RP. Medical acupuncture a holistic modality is reported to be effective in patients with RP but variable results in SRD. Besides acupuncture therapy, patient with chronic refractory RD or SRD may require additional treatment including conservative measures, conventional medications and surgical interventions.

Conclusion

Raynaud's disease, a complex clinical condition is commonly reported in females, presents with salient clinical features and needs management by means of a variety of therapies including medical acupuncture as there is no standard of care for both primary and secondary Raynaud's disease. Further rigor studies including randomized controlled trials are needed to fully understand the pathophysiology of Raynaud's disease and its treatment interventions in future.

Ethical Consideration: Not applicable

Conflicts of Interest: The authors declared no COI in this work

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