

What to do with troublesome hot flush?

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Hot flush (hot flush or facial flush) is the most frequent symptom experienced by women of peri-menopausal age. It may appear on women or even men after surgery or chemotherapy. Hot flush is one of the biggest reason for women to undergo hormone replacement therapy (HRT). It also crucially affects various aspects of life quality such as occupation, social life, daily routine and health awareness. The most effective and fundamental remedy for hot flush is HRT. However, a few women is not responsive to HRT and investigation to elucidate other causes of hot flush is warranted, especially in elderly. The contraindications such as breast cancer mandates other modality of treatment. Variety of treatment for hot flush other than HRT will be discussed herein.

Key Words: Hot flush, Treatment

I. Hot flush

A. Definition

Hot flush is a subjective feeling of warmth often associated with dilatation of cutaneous vessels and decrease of core temperature. It is often accompanied by sweating, tachycardia, anxiety, hypersensitivity or even panic. It typically lasts for several minutes although it ranges from seconds to over ten minutes and the frequency and intensity varies among individuals. Aura often appears before impending hot flush and is not identical to the hot flush itself. It is usually described

as 'sickness', 'agitation', 'numbness', or 'head tightness'. It lasts for about 5 to 60 seconds and tachycardia or increase of cutaneous vascular flow may temporarily appear.

B. Incidence

Hot flush may appear even before the menopause. Korean women are reported to experience hot flush in 70% which is the most frequent symptom of menopause and 60% of those who had hot flush replied the symptom began before the menopause.¹ Daily routine is compromised in 10% who undergo hot flush due to its intensity.

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Hot flush typically begins immediately after the last menstruation. It is frequent for the first 2 years in case of natural menopause and gradually subsides subsequently. Surgical castration triggers intense hot flush in a few weeks after the surgery. Those who receive tamoxifen as a treatment for breast cancer are reported to undergo severe and frequent hot flush for the first 2 to 3 months followed by gradual decrease and stabilization. Hot flush usually lasts for several months although it may persist for years.

C. Risk factors

Serum estradiol or estrone level is reported to be lower in women who have hot flush, however the symptom varies individually even among those who have similar level of estrogen. Underweight, poor exercise, or smoking are risk factors after menopause which are related to low level of serum estrogen. However, SWAN study reported that perimenopausal women of 40 to 55 years of age and those whose BMI is over 27 are predictive factors for hot flush which may be explained as the compromised role of estrogen by the insulation of increased body fat followed by increased core temperature.² Hot flush also varies between ethnicity or culture. For instance, it is less frequent in asians and caucasian than in african Americans. Also, in a prospective study of women with natural menopause, hot flush was more frequent in women who had longer period of transition (51% vs. 39%).³ Further investigation is warranted regarding the relationship between

hot flush and other factors such as genetic factors, diet, or exercise.

D. Cardiovascular risk

Recent studies report that the risk of cardiovascular disease was high in women with menopausal symptoms such as hot flush. Women with hot flush showed the change of lipid metabolism characterized by high BMI, hypertension, high frequency of atherosclerosis, and decreased endothelium-dependent vasodilation.⁴

II. Pathophysiology

A. Estrogen withdrawal and hormonal change

Estrogen withdrawal rather than the low serum level of estrogen is regarded as the cornerstone of hot flush although the mechanism is not established. Oophorectomy before menopause is followed by sudden estrogen withdrawal and intense hot flush whereas gonadal dysgenesis such as Turner syndrome with intrinsically low estrogen level does not provoke hot flush. If a gonadal dysgenesis patient abruptly ceases estrogen replacement after months of hormone therapy, the hot flush may appear which shows the estrogen withdrawal is an important precipitating factor for hot flush.

Hot flush also accompanies other hormonal changes such as increase of LH, adrenocorticotrophic hormone, and GH before the symptom, or increase of cortisone which may follow after hot

flush appears. Other related hormonal changes are the decrease of average SHBG, increase of free androgen index, calcitonin gene-related peptide, and neuropeptide Y, though a direct evidence still lacks that these changes are related to hot flush.

B. Hypothalamus

Estrogen withdrawal is induced by the failure of central temperature control center while peripheral nerves, vessels or central nervous system were suspected to be involved. Hot flush is not known to be directly related to serum estrogen, FSH, or LH levels. Hot flush is related to the pulsatile change of LH although it does not always appear in every LH elevation. Moreover, hot flush is not decreased by LH depression with GnRH agonist and it is not triggered by LH stimulation with GnRH. These imply hot flush is not directly caused by LH pulse though these two might have certain relationship. Hypophysectomized women due to a tumor in hypophysis were reported to experience hot flush and this suggests that temperature center failure is related to the dysfunctional temperature control center of hypothalamus rather than the pituitary gland.⁵

Sweating and vasodilation is activated to promote heat discharge in hot flush. In human, it is medial preoptic area that temperature control center resides to undertake this function. Sweating and vasodilation is to maintain core temperature in the range so-called 'thermoregulatory zone'. A recent study reported minute core temperature

change 15 minutes before symptom in 60% of those who have hot flush.⁶ Also, the thermoregulatory zone moves downward in those with hot flush and the zone is narrower. Heat loss occurs only with 0.01 degree of increase in core temperature over thermoregulatory zone and menopausal women who have narrow homeostatic range of temperature easily loose heat only with minute change in core temperature before hot flush followed by series of symptoms. Dysfunctional regulation of core temperature is mediated by number of neurotransmitters such as norepinephrine, estrogen, testosterone, and endorphin.

C. Neurotransmitters

Norepinephrine is the most important neurotransmitter in lowering critical temperature and promoting heat loss. Serum levels of norepinephrine metabolites surge immediately after hot flush and the core temperature rises followed by heat loss when norepinephrine is injected into hypothalamus.⁶ The production and secretion of norepinephrine is depressed by endorphins and catecholamine which is estrogen metabolite in temperature control nucleus. Estrogen and testosterone also stimulates endogenous endorphin production hence directly and indirectly control norepinephrine secretion.

Another neurotransmitter, serotonin (5-HT), is important in controlling temperature regulation and related to multiple steps, time- and dose-dependent. Temperature control response seems dependent to certain serotonin receptor in brain.

Serotonin_{1a} (5-HT_{1a}) and 2a (5-HT_{2a}) receptors are two out of several serotonin receptors known to be closely related to temperature control. Serotonin 2a receptor induces heat loss and activated by increased serotonin eventually producing hot flush. However, when combined with serotonin 2c receptor, a negative feedback to 2a receptor occurs. This implies that the role of serotonin in temperature regulation has multiple and complex steps.⁷ In an animal model, hyperthermia was prevented by 5-HT_{2a} antagonist, whereas hyperthermia was induced by direct stimulation of 5-HT_{2a} receptor in rodents. On the contrary, peripheral injection of 5-HT_{1a} agonist lowered core temperature in rodents and human. These indicate that the balance between 5-HT_{1a} and 5-HT_{2a} receptor is crucial in adequate control of body temperature. Manifestation and activation of 5-HT receptor can be regulated by gonadal hormones and adrenal corticosteroid which suggests that serotonin is linked to other hormonal systems related to hot flush. Estrogen withdrawal leads to decrease in serum serotonin, increase in sensitivity of 5-HT_{2a} in hypothalamus. And under this condition, certain intrinsic or extrinsic stimulus increases serum serotonin and induces 5-HT_{2a} receptor, changes set-point of temperature control, and eventually hot flush appears.⁷ When hot flush appears, set-point is down-regulated and normal body temperature is identified as being higher than the new set-point, leading to the activation of temperature regulation mechanism to lose heat. When the core

temperature decreases, it stimulates heat preservation mechanism leading to the series of symptoms related to hot flush.⁸

D. Hot flush induced by factors other than menopause

Generalized diseases that accompanied by hot flush are carcinoid syndrome, mastocytosis, medullary thyroid carcinoma, pancreatic carcinoma, pheochromocytoma, and renal carcinoma. Neurotic hot flush may occur with anxiety, brain tumor, migraine, Parkinson's disease, or spinal-cord lesion. Opioids also are capable of inducing hot flush such as which are luteinizing hormone-releasing hormone agonists or antagonists, anti-estrogens, SERMs, or aromatase inhibitors. Hot flush may be related to alcohol or drug reactions such as aromatase inhibitor, bromocriptin, calcium-channel blockers, cephalosporin, cholinergic drugs, chlorpropamide, ketonazole, metronidazole, and nicotinic acid. Hot flush also may be related to dietary habit and food additives in conditions such as auriculotemporal syndrome, dumping syndrome, taste problem, hot beverages, monosodium glutamate, sodium nitrite and sulphites.⁹

Tests for differential diagnosis to rule out these conditions may be performed. For thyroid diseases, thyroid-stimulating hormone test, complete blood count for subacute and chronic infection, and C-reactive protein. For psychiatric disease or stress, patient stress questionnaire, complete blood count to rule out leukemia. Urine

vanillylmandelic acid (u-VMA) test to rule out pheochromocytoma or chromogranin a urine 5-hydroxy indole acetic acid (5-HIAA) test to rule out carcinoid may be needed. CT or MRI is warranted to rule out malignant tumors (Krause et al., 2015). If relationship with postmenopausal hormone deficiency is not certain, consultation to other department such as internal medicine or neurology should be considered.

III. Treatment

A. Medication

The current available treatments for hot flush are not purposed to 'cure' but to decrease frequency and intensity hence to relieve symptoms and to reduce discomforts in daily life. No wonder, hot flush easily comes back when the treatment is discontinued. The exact mechanisms of the medications currently used for hot flush are not elucidated and placebo are effective in cases.

Treatment for hot flush is classified by pharmacologic and non-pharmacologic.

Pharmacologic treatments are either hormonal or non-hormonal medications. Hormonal therapy includes single estrogen, combined estrogen and progesterone, estrogen agonists and antagonists, testosterone, biologic hormones and single progesterone. Single estrogens are transdermal patches of ultra-low dose, low dose and standard dose. For combined estrogen and progesterone, oral medroxyprogesterone acetate (MPA) 5 mg per

day as a standard dose and intrauterine levonorgestrel. For single progesterone, oral and depo injection form may be used. Non-hormonal medications include SSRI, SNRI, gabapentin, and clonidine. Paroxetine, fluoxetine, citalopram and sertraline are SSRI; and venlafaxine and desvenlafaxine are SNRI. Non-pharmacologic treatments are acupuncture, exercise, rest, yoga, horse-riding, phyto-estrogens, vitamin E and omega-3 fatty acids.¹⁰

1. Hormone therapy

Hormone therapy reduces hot flush in 80-90% of women.

1) Estrogen

Estrogen is by far the most effective treatment for hot flush and can be prescribed in first hand if the subject is without contraindications. It is based on that occurrence of hot flush is related to menopausal failure of ovarian function. The effect of estrogen treatment does not appear immediately and maximal effect sometimes occur after months. The effect of estrogen, especially conjugated equine estrogen, often persists for weeks after termination of the treatment which is attributable to the stored estrogen in fat tissue. Route of administration or formulation does not known to affect the estrogen effect on hot flush.

2) Progestin

Other hormones have been investigated for treatment of vasomotor symptoms in menopausal

women who do not want estrogen or has contraindications. MPA is non-estrogenic steroid and reported to have effect on reducing hot flush in placebo-controlled double-blind trials. When MPA 150 mg per month was subcutaneously injected, hot flush was significantly reduced in 90% while 25% in those who received placebo.¹¹ The reduction of hot flush was dose-dependent and irregular bleeding was the most frequent complication. Oral medication of MPA was less accompanied by complication. Daily oral MPA of 20 mg reduced hot flush by 76% which was significantly lower than 26% reduction in placebo group.¹² Megestrol acetate (MA), which is another progestin, is also effective for hot flush in dose-dependent manner. High-dose MA is an effective treatment for breast cancer, however low-dose progestin theoretically induces cancer growth and reported to increase incidence and recurrence of breast cancer, hence precaution is needed for breast cancer survivors.

2. Non-hormonal alternatives

1) New anti-depressants

Investigation of anti-depressants for hot flush originated from search for novel treatment for hot flush of breast cancer patients. Number of anti-depressants specific to various neurotransmitters have been reported to reduce hot flush. Paroxetine which is a selective serotonin reuptake inhibitor (SSRI) and venlafaxine which is a selective serotonin-norepinephrine reuptake

inhibitor (SNRI) are those most studied. Low-dose (7.5 mg) paroxetine is a non-hormonal agent which is SSRI and was approved by FDA in 2013. The frequency and intensity of hot flush was significantly decreased 4 and 12 weeks after administration of paroxetine and persisted until 24 weeks in depressive postmenopausal women who had hot flush and without history of breast cancer. Every SSRI is metabolized by cytochrome P450 (CYP2D6) and hence cross-reacts with other drugs which share the same metabolic pathway. Tamoxifen, which is a hormonal antagonist for breast cancer, is a typical example and SSRI is restricted in breast cancer patients who take tamoxifen. Fluoxetine and sertraline are another SSRI and preliminary test showed some effect over placebo. The exact mechanism of SSRI in treatment of depression is not elucidated. Depression is known to be related to decrease of 5-HT_{1a} receptor and increase of 5-HT_{2a} receptor, and serotonin pump is suppressed by SSRI administration followed by increase of serotonin concentration in synapse. Long-term anti-depressive treatment induces 5-HT_{1a} receptor and increase sensitivity in forebrain while suppresses 5-HT_{2a} receptor eventually decrease hot flush.

SNRI is a hormone alternative which slightly suppresses CYP2D6 and may be cautiously prescribed breast cancer patients who receive tamoxifen. In an early report, daily 12.5 mg of venlafaxine reduced hot flush in 50% of both men and women.¹³ A large scale placebo-controlled randomized phase III trial was performed for 4

weeks showed 40% and 60% reduction when 37.5 mg and 75 mg or 150 mg was used, respectively, which was effective in reducing hot flush while placebo group only showed 27% reduction.¹⁴ Side effects of venlafaxine includes dry mouth, anorexia, constipation, and nausea. Nausea usually disappears a week after administration. Though rare, the syndrome of inappropriate antidiuretic hormone (SIADH) was reported in elderly was reported. Loss of libido, orgasmic dysfunction was complained by 15% of subjects. On the contrary, another report showed increased sexuality score in 4 weeks of venlafaxine administration for hot flush, to improve sleep pattern, and relieve depression.

2) Gabapentin / Pregabalin

Gabapentin is a gamma-aminobutyric acid analogue and mainly used for epilepsy or neurogenic pain. It acts on calcium-channel to decrease hot flush though the exact mechanism is not known. Most studies utilized daily dose of 900 mg and hot flush was suppressed in 42-73% in phase 2 study, however further investigation is needed.¹⁵ Common side effects includes drowsiness, disorientation, headache, and peripheral edema. Also, when 75 mg and 150 mg of pregabalin was administered twice a day for 6 weeks, hot flush was significantly reduced in 65% ($P = 0.009$) and 71% ($P = 0.007$), respectively.

3) Clonidine

Clonidine is a centrally acting alpha-adrenergic

receptor agonist and mainly used as a anti-hypertensive by affecting vascular responsiveness. Daily oral dose of 0.1 mg of clonidine substantially reduces the frequency and intensity of hot flush in dose-dependent manner.¹⁶ Dry mouth is the most common side effect and insomnia, headache, depression, and nausea may occur, hindering from wide prescription.

4) Veralipride

Veralipride is a benzamide derivative and has anti-dopaminergic and anti-gonadotropic effect. Veralipride is effective on hot flush by suppressing norepinephrine secretion mediating endorphin. Daily dose of 100 mg was effective on hot flush in placebo-controlled study and effects which was similar to estrogen was observed in some subjects. The compliance was comparable to estrogen however some complained of breast tightness, galactorrhea, gastrointestinal symptoms, fatigue, and dyspnea. Also, the study reported increased dehydroepiandrosterone sulphate (DHEAS) when veralipride was administered along with increased serum estradiol to the level of 10 days after menstruation in postmenopausal women. However the authors indicated that hot flush reducing effect is not related to the estradiol increase but to the anti-dopaminergic action of veralipride. Therefore, the advantage of veralipride over estrogen in postmenopausal women still lacks ground even if it has comparable compliance and increase of serum estradiol.

5) Bellergal

Bellergal is a mixture of belladonna alkaloids, ergotamine tartrate and phenobarbital. Bellergal significantly reduced hot flush in 60% compared to 22% of placebo although sedation, dry mouth, dizziness, and vertigo was common in placebo-controlled trial.¹⁷

B. Non-pharmacologic treatment

1. Tolerance and behavior modification

Postmenopausal women who suffer from hot flush usually seeks ways to soothe the symptom and avoid from stressful conditions. Such methods includes keeping cool temperature in the room, utilizing air conditioner, and refraining from irritative food such as hot or spicy food, alcohol, or caffeine. Intentional paced respiration 6 to 8 times a minute, exposing to cool air, yoga, meditation, or regular exercise is helpful when a prodromal aura of hot flush appears.

2. Vitamin E

Vitamin E is one of the most popular care. However, reduction of hot flush was not remarkable (22% vs. 25%) in a placebo-controlled trial.¹³ Notable side effect was not reported.

3. Herbal

Phytoestrogen, black cohosh, dong quai, evening primrose, seed oil, and ginseng have been traditionally prescribed to ease hot flush. However, these traditional herbal medicines lack

an evidence of effect on postmenopausal vasomotor symptoms such as hot flush.

CONCLUSION

The treatment of hot flush starts from accurate diagnosis. Every aspect of life in postmenopausal women should be taken into account such as intensity and frequency of hot flush along with sleep pattern, daily routine, and occupation.

If the hot flush is tolerable that it does not affect daily routine, soy bean, isoflavon, black cohosh, or vitamin E may be primarily recommended. If sleep or daily life is compromised by hot flush, hormone replacement therapy is most effective, if not contraindicated. If estrogen is contraindicated or reluctant to hormonal drugs, single progesterone, SSRI/SNRI such as paroxetine, venlafaxine, gabapentine or pregabalin. A consent along with detailed explanation on effect and advantages/disadvantages is mandatory when medications including estrogen is prescribed. The symptom should be evaluated periodically and the duration of treatment be adequately determined because hot flush gradually vanishes.

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Peer Reviewer's Commentary

Hot flush is the most frequent symptom experienced by women in the perimenopausal period, and it crucially affects various aspects of life quality such as occupation, social life, daily routine and health awareness. This review well summarized the overall knowledge of the hot flush including definition, pathophysiology, and treatment.