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Mini review

To bee or not to bee: The potential efficacy and safety of bee venom acupuncture in humans

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ABSTRACT

Bee venom acupuncture is a form of acupuncture in which bee venom is applied to the tips of acupuncture needles, stingers are extracted from bees, or bees are held with an instrument exposing the stinger, and applied to acupoints on the skin. Bee venom is a complex substance consisting of multiple anti-inflammatory compounds such as melittin, adolapin, apamin. Other substances such as phospholipase A2 can be anti-inflammatory in low concentrations and pro-inflammatory in others. However, bee venom also contains proinflammatory substances, melittin, mast cell degranulation peptide 401, and histamine.

Nevertheless, in small studies, bee venom acupuncture has been used in man to successfully treat a number of musculoskeletal diseases such as lumbar disc disease, osteoarthritis of the knee, rheumatoid arthritis, adhesive capsulitis, and lateral epicondylitis. Bee venom acupuncture can also alleviate neurological conditions, including peripheral neuropathies, stroke and Parkinson's Disease. The treatment has even been piloted in one series to alleviate depression.

An important concern is the safety of bee venom. Bee venom can cause anaphylaxis, and several deaths have been reported in patients who successfully received the therapy prior to the adverse event. While the incidence of adverse events is unknown, the number of published reports of toxicity is small. Refining bee venom to remove harmful substances may potentially limit its toxicity.

New uses for bee venom acupuncture may also be considered.

1. Introduction

Bee venom acupuncture is form of acupuncture in which bee venom is applied to the tips of acupuncture needles, stingers are extracted from bees, or bees are held with an instrument, such as a forceps, squeezed to cause the stinger to emerge from the lower abdomen, and then either the needles or stinger is applied acupoints on the skin (Bogdanov, 2017). Bee venom itself is a complex compound consisting of multiple components, some of which are surprisingly anti-inflammatory and anti-nociceptive despite the well-known pain of a bee sting (Bogdanov, 2017; Cherniack, 2010). While the venom itself consists of more than fifty components, the most common constituent, melittin, is anti-inflammatory, as are other components, apamin, adolapin, and (low concentrations of) phospholipase A2 (Bogdanov, 2017; Cherniack, 2010; O'Connor and Peck, 1980). A recent review, which summarized research on animal models and potential applications, outlined the beneficial physiologic mechanisms of bee venom as suppressing inflammation, and altering cellular gene expression, apoptosis, and fibrosis (Zhang et al., 2018). However, bee venom also consists of many proinflammatory compounds, such as higher doses of phospholipase A2, mast cell degranulation peptide 401, hemolytic compounds, including melittin, and allergenic substances, such as several protease inhibitors and peptides (Bogdanov, 2017). Thus while the healing potential is present, the potential for side effect and allergic reaction certainly exists (Bogdanov, 2017).The risk of harm was underscored by a recent report of a Spanish women who died of an anaphylactic response to live bee acupuncture (Vazquez-Revuelta and Madrigal-Burgaleta, 2018).

The purpose of this manuscript is to outline the published medical literature regarding the potential of bee venom acupuncture to treat disease in man, and the documented harms (with reference to animal studies when appropriate). Potential references were identified from the PubMed reference database using search terms such as “bee venom,” “acupuncture,” and “apitherapy”.

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Some investigations have attempted to establish the mechanism by which bee venom acupuncture may act. In one study, researchers injected various substances into a paw acupoint of rats followed by a proinflammatory substance with or without bee venom (Chen et al., 2010). Preadministration of the acupoint with capsaicin attenuated the activity of bee venom in reduction of inflammation, suggesting that bee venom substances act through capsaicin-responsive pain pathways.

Other studies imply the involvement of other neural pathways, such as spinal alpha pathways. After causing an induced injury to a rat's paw, researchers blocked bee venom relief of thermally-created pain with an alpha-2-adrenergic antagonist, idazoxan, suggesting a role for spinal alpha-2-adrenergic receptors in pain perception (Roh et al., 2004). In another rodent pain model trial, clonidine, an alpha-2-receptor agonist, enhanced the effect of bee venom apipuncture in reducing experimentally induced rat paw pain (Yoon et al., 2009). When rats received idazoxan, the synergistic effect of clonidine and bee venom attenuated.

Idazoxan suppressed bee venom acupuncture relief of peripheral neuropathy in rats induced by a chemotherapy drug, paclitaxel, but the alpha-1-receptor antagonist prazosin had no effect (Choi et al., 2017). An alpha-2-receptor-antagonist, yohimbine, blocked the pain-relief induced by bee venom in neuropathic murine paw pain induced by another chemotherapeutic agent, oxaliplatin (Yeo et al., 2016). Two other adrenergic antagonists, phenotolamine and idazoxan, inhibited the pain alleviating effect of acupuncture in an oxaliplatin induced rat pain model (Lim et al., 2013).

Additional neural pathways may mediate the effect of bee venom. Methylsergide, which antagonizes serotonin receptors, blocked the effect of bee venom acupuncture in a rat paw pain model, implying serotoninergic mediation of the effect of bee venom (Kim et al., 2005). CT imaging of rodent brains during bee venom acupuncture also revealed activation of catecholaminergic brain pathways as well (Kwon et al., 2004). Furthermore, one study implied a role for nicotinamide receptors. In a rat pain model in which neuropathic injury had been induced by the chemotherapy drug oxaliplatin, the serotonin-depleting substance DL-p-chlorophenylalanine prevented pain relieve by bee venom acupuncture (Lee et al., 2014a). An additional investigation of oxaliplatin-induced rat pain, nicotinic receptor antagonists methyllycaconitine and erythroidine hydrobromide attenuated the effect of bee venom acupuncture on an injured rat's paw exposed to cold (Yoon et al., 2015). In one study, mice that had experimentally induced neuropathy caused by the chemotherapy agent oxaliplatin (Kim et al., 2016). When the pain was exacerbated by cold or mechanical stress to the paw, injections of 0.25–1 mg/kg morphine relieved the pain, but the relief was increased by acupuncture combined with 0.25–2.5 mg kg bee venom, and the opioid antagonist naloxone decreased pain relief.

The neurologic mediation of analgesia by bee venom acupuncture may be specific to the type of pain induced. In a rat model in which investigators induced osteoarthritis by administration of collagenase to the knee, bee venom injected into acupoints achieved greater pain relief into other non-acupoint sites. Opioid and adrenergic receptor agonists did not improve analgesia, but δ-opioid antagonist and α_2 adrenergic receptor antagonists attenuated analgesia (Huh et al., 2018).

Another mechanism by which bee venom acupuncture relief pain is through its effect on cytokine concentrations. Rats subjected to experimental spinal cord injury then subjected to bee venom acupuncture at acupoints developed a decrease in serum concentrations of the proinflammatory cytokines IL-6 and IL-1β, while increasing concentrations of anti-inflammatory cytokines IL-4, and IL-10 (Nascimento de Souza et al., 2017). Rats also performed better on a test of locomotor function after bee venom acupuncture.

2. Musculoskeletal pain

On important application for bee venom acupuncture may be to treat musculoskeletal pain. In a relevant animal experimental pain, models, investigators who created arthritic pain in rats through the injection of collagen derived from cows, mitigated the rodents' discomfort using apipuncture. The α_2 receptor antagonist yohimbine quelled the response to acupuncture. Furthermore, another animal pain model investigation noted that bee venom inhibited pain in true acupoints better than non-acupoints (Kwon et al., 2001).

A metaanalysis one decade ago of bee venom acupuncture use for musculoskeletal pain found no more than four appropriate studies in each form of, but noted that bee venom acupuncture alone or in combination with traditional acupuncture was superior to traditional acupuncture alone at pain relief, and in particular, for herniation of lumbar discs (Lee et al., 2008). In a recent human trial, fifty-four people, blinded to group assignment mean age 50, experienced treatment with bee venom or sham acupuncture. Participants obtained six treatments over three weeks from an acupuncturist also blinded to substance placed on the needle tips. Those subjects receiving bee venom experienced a 26% reduction on pain on a visual analog scale after three weeks ($p < 0.05$) (Seo et al., 2017). Forty dogs, evaluated by veterinarians to have thoracolumbar disc diseases and needled twice weekly with 20μ bee venom in addition to usual treatment (prednisone and the non-steroidal anti-inflammatory agent carprofen) or usual treatment alone for 1.5 months (Tsai et al., 2015). Bee venom acupuncture significantly lowered veterinarians ratings of animal pain on a six point scale in animals with moderate (mean score 3.43 to 0.98, $p = 0.001$) or severe pain (5–3.40, $p = 0.002$) where as usual treatment did not significantly alleviate pain.

Researchers also utilized bee venom acupuncture to alleviate osteoarthritis pain in the knee. Sixty-nine Korean subjects received either bee venom (0.05 ml of a 1: 10,000 dilution) injections to a joint intrajoint acupoint injection, or both biweekly for nine injections (Lee et al., 2012). Subjects in all three groups obtained an approximately thirty percent improvement, in pain and function (68 point WOMAC [Western Ontario and McMaster University Osteoarthritis Index] score, $p = 0.0001$).

Other studies, not randomized controlled trials, imply a role for bee venom acupuncture in the treatment of other musculoskeletal disorders. In a retrospective study of the effects of bee venom acupuncture on adhesive capsulitis, a telephone survey of subjects, who received either both bee venom acupuncture and physical therapy, bee venom acupuncture, or physical therapy with a saline injection, for adhesive capsulitis of the shoulder. Individuals receiving both treatments reported significantly better mean pain and function on the 130-point SPADI pain and disability index (13.57 for both treatments vs 4.35 for physical therapy alone; $p = 0.043$) (Park et al., 2014). One case series also suggested that bee venom acupuncture may alleviate lateral epicondylitis. Among twenty Korean patients who experienced a combination of acupuncture with heated needles *(hwachim)* and bee venom acupuncture for as many treatments as patients required based on their condition, pain on a visual analog scale decreased from a mean 10/10 to 4/10 ($p = 0.000$) (Jung et al., 2014).

3. Neuropathic pain

Several studies suggest bee venom acupuncture might be used to treat neuropathic pain. In one animal studied, previously cited, bee venom acupuncture treated cold-induced neuropathic pain (Roh et al., 2004). In addition, rats with experimental spinal cord injury obtained significantly greater pain relief when bee venom was injected into a paw acupoint (Kang et al., 2015). Two case series documented the effect of bee venom acupuncture on neuropathy resulting from chemotherapy. In one, eleven participants obtained six acupuncture sessions in twenty-one days. Mean pain scores on a one to ten visual analog scale decreased from a mean of six to 2.63 ($p < 0.05$) (Yoon et al., 2012). In a second case series, four people who received three treatments over seven days experienced a decline on the ten-point visual analog scale from a mean of 8.75 to 2.75 (Park et al., 2012).

4. Neuropsychiatric disorders

Another role for bee venom acupuncture has been to alleviate neuropsychiatric disorders. Bee venom acupuncture improved hematologic parameters in a rodent model of amyotrophic lateral sclerosis. In one study, bee venom acupuncture at a tibial acupoint (0.1 μg/g body weight) every second day for fourteen days prevented reductions in neuron number in brain section slices (Cai et al., 2015). In another, anti-inflammatory enzyme cyclooxygenase 2 and Iba-1 concentrations increased in hepatocytes, splenocytes, and nephrons after treatment at a tibial acupoint with bee venom acupuncture (Lee et al., 2015a). The enzyme concentrations did not increase in mice injected intraperitoneally with saline alone (Lee et al., 2015a).

An additional trial of bee venom acupuncture in mice suggested it might be useful to treat methamphetamine dependence (Kim et al., 2011). Mice given methamphetamine received bee venom at concentrations of 0.01 mg/ml exhibited a lower body temperature and greater locomotor activity than those that received saline acupuncture alone.

Human trials of bee venom acupuncture show bee venom improved human subjects' assessments of function in Parkinson's disease. One study used bee venom acupuncture as an adjunctive therapy for Parkinson's in a double-blinded controlled trial. Seventy-three individuals already on conventional medications for Parkinson's obtained bee venom acupuncture sessions with 1 mg bee venom in 20 ml saline every other day for three months or placebo acupuncture with saline. Those participants that experienced bee venom acupuncture received a small (1.16 points/101) but statistically significant ($p = 0.001$) improvement in Parkinson's disease rating scale scores (UPDRS II + III) for activities of daily living and gait (Cho et al., 2018). Another unblinded trial provided actively treated subjects with Parkinson's disease bee venom acupuncture with 0.005% bee venom in saline every other day for three months. Participants improved their Parkinson's disease rating scores by a mean 27 points ($p < 0.05$) (Doo et al., 2015).

An additional trial suggested a benefit for stroke patients. Sixteen subjects obtained acupuncture injections of 0.005% bee venom in saline or saline alone into acupoints biweekly for twenty-one days to relieve pain (Cho et al., 2013). The mean visual analog pain score decreased in the bee venom treated group from a mean of 72 out of 100 to 35.5 ($p < 0.007$) while no significant change occurred in the control group.

One use of bee venom acupuncture in neuropsychiatric disorders has been to treat depression. In one case series, thirty-seven depressed subjects, rated by the Beck's Depression Scale, “twenty-one rated as moderately depressed” (19–29 points/63) and five as “severely depressed” (> 30 points) (El Wahab, 2015). Subjects received live beestings to multiple acupoints, twice a week. At the end of one year, none were depressed.

Finally, in a case report, bee venom acupuncture treated a neurofibroma. A clinician injected sweet bee venom (venom processed by gel filtration chromatography and propionic acid/urea polyacrylamide gel electrophoresis to separate away potential allergens) through acupuncture 20 ml every two weeks (concentration not stated) for four years (Lim et al., 2014).During that interval, the authors claim that the neurofibromas on her right pelvis stopped growing, and the range of motion in her right hip increased.

5. Autoimmune disorders

Bee venom acupuncture has also been used to treat autoimmune disorders. In a mouse model of atopic dermatitis, induced by trimellitic anhydride, bee venom acupuncture created favorable immunological responses (Sur et al., 2016). After trimellitic anhydride had been injected into the skin, bee venom injections with an insulin needle of 0.3 mg/kg into an acupoint resulting in lower concentrations of the proinflammatory cytokines IL-4 and IgE, than at a non-acupoint. In another experiment, using a rodent model of autoimmune encephalitis, researchers injected 0.25–0.8 mg/kg bee venom or saline into an acupoint or control acupoints before exposure to the agent used to induce autoimmune toxicity (Lee et al., 2016). Brain sections of animals pretreated with bee venom exhibited reduced neuronal loss and inflammatory cell infiltration.

In man, investigators have used bee venom acupuncture to treat rheumatoid arthritis. A systematic review of the effects of bee venom acupuncture produced just one study meeting search criteria (Lee et al., 2014b). In that investigation, subjects with rheumatoid arthritis obtaining twice monthly acupuncture for eight weeks experienced a significantly mean lesser pain on a visual analog scale (16.9/100), and fewer swollen and tender joints (Lee et al., 2003).

6. Safety

An important concern with bee venom acupuncture has been its safety. To date, no systematic analyses have been conducted on safety in clinical practice, although there have been a number of reports of adverse reactions to bee venom acupuncture. In the most recent published case of a death, a woman developed anaphylaxis after safely experiencing monthly bee venom acupuncture treatments for two years. The victim had no history of any medical disorders, reaction to bee stings, or allergies. Desiring relief from “muscle contractures” and “stress”, she developed acute shock suddenly during a treatment and died.

One previous case of a fatality involved a sixty-five year-old woman, who experienced disseminated intravascular coagulation during a second acupuncture session following an initial treatment without incident (Jung et al., 2012). She suddenly developed symptoms, one half-hour after the treatment, and died a day later of hypovolemic shock.

Fortunately, these are the only two reported cases of deaths due to bee venom acupuncture in the published scientific literature. Descriptions of single persons after uneventfully previously treatment developing acute anaphylactic shock responding to treatment (Jo and Roh, 2015), Guillaume- Barre syndrome (which led to two months stay in an intensive care unit, but the patient was ultimately released, months later without deficit) (Lee et al., 2015b), an irreversible ulnar nerve injury (Park et al., 2017), thrombocytopenia with ecchymoses (Abdulsalam et al., 2016), an “acute lung injury,” (Chae et al., 2015) and a *M chelonae* infection (Cho et al., 2014) have been reported. Other individual adverse events noted include arrhythmia (Cheng, 2004), stroke (Huh et al., 2008; Park et al., 2000), nephrotic syndrome (Kim et al., 2007), pulmonary edema (Karapata, 1961), liver failure (Zhong et al., 2005), hepatitis (Pijak, 2011), and uterine contractions (Karakurt et al., 2010).

In addition, individual case reports cite dermatologic complications. A collective summary of dermatological case reports of adverse events with acupuncture noted that bee venom acupuncture was the frequent form of acupuncture in such complications (13 of 25 cases) (Park et al., 2016). These included local anaphylactic skin reactions, an abscess, pyoderma, lipoatrophy, and foreign body granuloma (Park et al., 2016). Other reports of skin reactions include a case of chronic folliculitis (Lee et al., 2013) and giant dermatofibroma (Rhee et al., 2009).

To date, although no systematic study has evaluated the safety of bee venom acupuncture in clinical practice, or even recorded the prevalence or incidence of adverse events, one systematic metaanalysis recorded adverse events in published trials and case reports. In that investigation, the incidence of adverse events was 28.87% or a relative risk of 3.61 (95% CI 2.10–6.20) compared to parenteral saline administration (Park et al., 2015). Furthermore, research has not identified the possible risk factors for adverse sequelae to bee venom acupuncture, such as dose, frequency, site, or form of administration (e.g., live bee vs acupuncture needling). Thus, despite the two deaths, and the metaanalysis suggesting increased risk, no firm conclusions can be drawn about safety from the published scientific literature in the absence of large-scale investigations of safety in clinical use. The suggestion of

Table 1
Summary of cited studies.

Topic/study	Species	Size (N)	Summary
Lumbar disc disease			
Seo et al. (2017)	Human	54	Single-blind, BVA = 26% reduction in pain on visual analog scale over 3 mos ($p < 0.05$)
Tsai et al. (2015)	Dog	40	Reduction of pain assessment (32% in severe pain, 72% in moderate pain) ($p = 0.001$)
Knee osteoarthritis			
Lee et al. (2012)	Human	69	Improvement in WOMAC score ($p = 0.0001$)
Rheumatoid arthritis			
Lee et al. (2003)	Human	40	Improved tender & swollen joint count ($p < 0.0001$. $p = 0.05$)
Adhesive capsullitis			
Park et al. (2014)	Human	25	Reduction in pain and disability index w/PT (13.57) vx PT alone (4.35) ($p = 0.043$)
Lateral epicondylitis			
Jung et al. (2014)	Human	20	Reduction in pain on visual analog scale from 10 to 4 ($p = 0.000$)
Neuropathic pain			
Yoon et al. (2012)	Human	11	Reduction in pain on visual analog scale from 6 to 2.63 ($p < 0.05$)
Park et al. (2012)	Human	4	Reduction in pain on visual analog scale from 8.75 to 2.75
Parkinson's Disease			
Cho et al. (2018)	Human	73	Improvement in UPDRS scale score ($p = 0.001$)
Doo et al. (2015)	Human	11	Improvement in UPDRS score by 27 points ($p < 0.05$)
Stroke			
Cho et al. (2013)	Human	16	Pain by visual analog score from 72 to 35.5 ($p < 0.007$)
Depression			
El Wahab (2015)	Human	26	Full recovery from depression

heightened adverse effects experimentally and anecdotally should prompt such investigations.

7. Future directions and conclusions

Despite a number of investigations and a couple of systematic reviews (see Table 1), it is difficult, as with safety, to ascertain with certainty the efficacy of bee venom acupuncture in treating health disorders. Thus far, bee venom acupuncture demonstrates greatest promise in the treatment of musculoskeletal disorders and Parkinson's disease, but rigorously designed scientific trials remain to be performed. In addition, in most cases, the optimal dose, frequency duration, and form of bee venom still need to be determined for optimum effect and safety.

Newer forms of bee venom delivered with the acupuncture needle might improve safety. In one instance, researchers modified bee venom by extracting out what they deemed the most likely allergenic substances, histamine and enzymes, creating what they termed “essential bee venom.” (Ahn et al., 2016) They treated 20 normal adults with either essential or natural venom by acupuncture and observed that, while subjects generally did not experience less pain, those injected with essential bee venom noted significantly less swelling and itching after one to two days (80% after one day) (Ahn et al., 2016). Essential bee venom induced an 83% smaller erythematous wheal at the injection site after one day. Furthermore, delivery of individual components of bee venom, such as melittin, may be more effective and safer than whole bee venom.

In addition, there may be additional uses for bee venom acupuncture. One of these might be gouty arthritis. A preliminary study of rats indicated that intradermal administration of bee venom as a gel transdermally with a microneedle resulted in decreased inflammatory response as measured by nitric oxide release (Zhao et al., 2016).

Other possible uses of bee venom might be extended to bee venom acupuncture. Bee venom, and its components, particularly melittin (Rady et al., 2017), have been tested in vitro for antineoplastic potential in leukemia (Mohseni-Kouchesfahani et al., 2017; Safaeinejad et al., 2013; Moga et al., 2018), lung (Moga et al., 2018; Zhang and Chen, 2017), ovarian (Moga et al., 2018; Jo et al., 2012), liver (Moga et al., 2018; Liu et al., 2008), prostate (Moga et al., 2018; Park et al., 2011), breast (Moga et al., 2018; Ip et al., 2008), and bladder cancer (Moga et al., 2018; Jin et al., 2018), and in animal models at treatment for bacterial infections (Fratini et al., 2017), such as prostatitis (Lin et al., 2017), and chronic kidney disease (An et al., 2016). Future in vitro and in vivo testing should further establish more definitively the role of bee venom acupuncture in the treatment of disease.

Ethical statement

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