The Development of an Effective Herbal, Non-Opioid-Based Therapy to Treat Acute Post-Operative Pain

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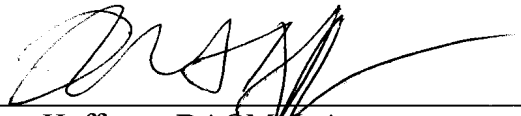

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Abstract

The opioid crisis is a national epidemic which continues to claim the lives of thousands of Americans. Many become dependent on opiates following an injury or surgery. Thus, it is imperative to develop safe and effective non-opioid-based therapies for pain management. Traditional Chinese Medicine has been around for millennia and its herbal pharmacopeia has a long history of analgesic use. Numerous studies of individual herbs have been conducted in rodent models, however, human trials using a compounded herbal formula are lacking in Western medical literature. **Method:** The current study is a prospective, randomized, double-blind, controlled clinical trial in which a combination herbal therapy was administered to half of the 48 study participants (experimental arm, n=24) and a medically inert substance was administered to the other half of the participants (control arm, n=24). All participants were undergoing low risk outpatient surgeries such as abdominal or pelvic hernia, vasectomy, vasectomy reversal, varicocele repair, or sperm retrieval. They received the standard medical treatment including Acetaminophen, Non-Steroidal Anti-Inflammatory Drug (NSAID) and prescription opioid medication. **Results:** The experimental herbal formula was determined to be safe to use pre and postoperatively, however, it was not found to effectively treat acute postoperative pain nor lower opioid analgesic consumption.

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Chapter One: Introduction

The abuse of prescription opioids has been rapidly increasing over the past 20 years, from 76 million prescriptions filled in the U.S. in 1991 up to 219 million prescribed in 2011 (Compton, Boyle, & Wargo, 2015). Such widespread prescription has contributed to opioid abuse, with 10.3 million Americans aged 12 or older reporting nonmedical use of prescription opioids in 2018 (*2018 National Survey on Drug Use and Health)*. Although prescription drug monitoring programs and the National All Schedules Prescription Electronic Reporting Act have contributed to substantial reductions in opioid prescriptions (Cantrill et al., 2012), death by opioid overdose continues to climb at a staggering rate. Between 1999 to 2017, death by opioid overdose increased four-fold. According to the Center for Disease Control and Prevention, in 2017, 70,000 people died of drug overdoses, making it a leading cause of injury-related death in the U.S. Sixty eight percent of those deaths involved a prescription or illicit opioid. Adults between the ages of 25-54 had the highest rates of drug overdose deaths. The age adjusted rate for drug overdose in 2017 was 9.6% higher than it was in 2016 (Hedegaard, Miniño & Warner, 2018).

Some believe that health care providers are in part to blame for the opioid crisis. When compared to the rest of the world, the U.S. prescribes 50 times more opioids. Perhaps not all of these prescriptions are necessary. For example, Barham et al. (2019) found that post-vasectomy there was no significant difference in scrotal pain for opioid and non-opioid groups. However, three to six months later, 7.8% of the opioid group reported persistent use compared to 1.5% of the non-opioid group. Research shows that a single day's prescription alone is enough to lead to opioid dependence. Shah et al. (2017) tracked 1.3 million opioid-naïve adults who were discharged from the hospital with a new opioid prescription. One year later, 6% of those given a

single day's prescription reported persistent opioid use and that rate increased to 13.5% with prescriptions for seven days or more. With few safe and effective non-opioid alternatives, the death toll will continue to rise. This public health crisis presses for tremendous opportunities to develop appropriate and effective solutions. For instance, the use of non-opioid pain relievers (e.g., acetaminophen, NSAIDs) in postoperative settings can reduce chronic pain and opioid consumption (Brubaker, Kendall, & Reina, 2016). Herbal medicine can also be a valuable non-prescription alternative.

For thousands of years China has used herbal medicine to treat pain, trauma, and even for surgery. Hua Tuo was a skilled acupuncturist, diagnostician, and was revered as the God of Surgery. He is believed to be born in 190 AD and lived to be 100 years old. He is said to have performed complex abdominal and back surgeries using a general anesthetic *ma fei san* (numbness powder). Modern authors believe *ma fei san* to be a narcotic formula containing opium, hashish, and aconitum tubers. When he was finished operating, he applied a salve or ointment to the wound and gave the patient an herbal medicine. According to the *Hou Han Shu* (History of the later Han): "For the internal diseases that needles and medicine are unable to reach, administer *ma fei san* together with alcohol. When the patient loses consciousness make incisions in the abdomen or back to excise the accumulations and masses (and the patient) will recover within a month." Hua Tuo is believed to have used mulberry bark fibers as sutures for the wounds after surgery (Buck 2014). One of the most famous stories tells Hua Tuo operating on Kuan Kung, a famous general of the Three Kingdoms. Hua Tuo is said to have operated without anesthesia while Kuan Kung played chess, removing a poisoned arrow from his arm. Unfortunately, Hua Tuo burned all of his manuscripts before his death and we have no record of the herbs used in the salves, ointments, or medicine used in surgery (Wong & Wu, 1977).

In order to discuss the etiology of pain in Traditional Chinese Medicine (TCM), we must first understand the concept of Qi. The character for Qi indicates that it is something that is both material and immaterial. It can mean "vapor," "gas," "steam" or uncooked "rice." Qi can be as rarefied and immaterial as vapor or as dense and material as rice. This indicates that Qi is a subtle substance (steam, vapor) that is derived from a coarse one (rice), just as steam is produced when cooking rice. Some of the various translations for Qi include: "energy," "material force," "matter," "ether," "matter-energy," "vital force," "life force," "vital power," and "moving power." Since Qi has such a versatile nature and can assume different manifestations and be different things in different situations, it has made it very challenging to translate. In TCM, the body and mind are nothing but forms of Qi, which is at the basis of all. All vital substances are manifestations of Qi in varying degrees of materiality, ranging from body fluids, which are completely material, to the mind (shen), which is completely immaterial (Maciocia, 1989).

Now that we have a basic understanding of Qi, it is possible to discuss the etiology of pain in TCM. Pain is the stagnation of Qi, stagnation of blood or both. It is often said, "that where there is pain, there is stagnation; where there is stagnation, there is pain." Physical trauma when mild can cause stagnation of Qi and the pain is marked by distention with no fixed location. More severe physical trauma including surgery will cause stagnation of blood as well. Pain due to blood stagnation has a stabbing, boring quality and a fixed location in a small area. Often physical trauma can lead to *Bi Zheng* or Painful Obstruction Syndrome, which is a swelling of the joints often associated with arthritis (Maciocia, 1989).

Since pain and physical trauma in TCM are due to the stagnation of Qi, blood or both, herbs in the TCM pharmacopeia for pain relief focus on activating Qi and blood to remove stasis. TCM has used various plant extracts for pain management. One of the most potent herbs for

pain relief is *Yan Hu Suo* (Rhizoma Corydalis), its use dates back to 741 A.D. *Yan Hu Suo* (Rhizoma Corydalis) activates Qi and blood circulation to relieve pain from a variety of causes in all parts of the body. Another powerful herb to alleviate pain is *Mo Yao* (Myrrh). It treats traumatic injuries with bruising, *Bi Zheng,* as well as reduces swelling and generates flesh, enhancing the healing of skin lesions and ulcerations. This herb activates blood circulation and its use dates back to 600 A.D. *Mo Yao* (Myrrh) is clinically used in conjunction with *Ru Xiang* (Frankincense) to have a synergistic effect in relieving pain. *Ru Xiang* (Frankincense) treats the same conditions as *Mo Yao* (Myrrh) and also alleviates pain by activating blood circulation. Its use dates back to 500 A.D. *Xiang Fu* (Cyperi Rhizoma) activates Qi and is used to treat hypochondriac, epigastric, abdominal, hernial, and menstrual pain. *Xiang Fu* (Cyperi Rhizoma) has been used since 500 A.D. *Da Zao* (Fructus Jujubae) tonifies the Spleen and Stomach and benefits Qi to improve digestion, tonifies blood, and calms the *Shen* (mind) for irritability, insomnia, and emotional instability. *Da Zao* (Fructus Jujubae) also harmonizes the harsh or toxic effects of other herbs in a formula. The use of *Da Zao* (Fructus Jujubae) dates back to the second century (Chen & Chen, 2001).

TCM herbal formulas are complex recipes of medicinal substances. They are not a simple collection of ingredients in which the actions of the herbs are added together in a cumulative manner. The actions of one ingredient affect the actions of the others in the formula. It's the very complex interactions that make the formula so effective. Being that every medicinal substance has its strengths and shortcomings, an effective formula must be balanced to emphasize the strengths and minimize any side effects. The combination of substances in a formula often has a synergistic effect creating a new therapeutic agent, which can treat more effectively than a single substance.

The organizing principle essential to building an herbal formula is the hierarchy of ingredients. The primary herb which treats the principal pattern or disease is called the "Chief" herb. This herb is indispensable in the formula and has the highest dosage. The "Deputy" aids the chief herb in treating the principal pattern or disease and is the main ingredient used to treat a coexisting pattern or disease. The "Assistant" reinforces the function of the Chief or Deputy herbs or treats a less important aspect of the disease. It also moderates the toxicity or harsh properties of the other herbs. Lastly, it can have an opposite effect to the Chief herb, useful in complex disorders. The "Envoy" directs the actions of the formula to a certain channel or part of the body as well as harmonizes the actions of the other ingredients. Not all herbal formulas contain the full hierarchy of ingredients (Scheid et al., 2009).

Though the herbal formulas used by Hua Tuo for surgery, physical trauma, and pain have been lost, there are still many classical formulas that are used today. For example, *Shen Tong Zhu Yu Tang* (Drive Out Blood Stasis from a Painful Body Decoction) is used to treat generalized pain throughout the body due to Qi and blood stagnation as well as *Bi Zheng.* This formula among other herbs contains *Mo Yao* (Myrrh) and *Xiang Fu* (Cyperi Rhizoma). A formula for external injuries and trauma is *Qi Li San* (Seven-Thousandths of a Tael Powder). This formula relieves pain and stops bleeding by activating blood circulation and dispersing blood stasis. It contains the paired herbal combination of *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) to strongly activate blood. *Xing Qi Huo Xue Tang* (Move Qi Invigorate Blood Decoction) treats traumatic injury, painful bruises on the body, dysmenorrhea as well as broken tendons and bone fractures. It stimulates blood circulation to eliminate stasis and activates the flow of Qi to eliminate swelling and pain. This powerful formula contains *Xiang Fu* (Cyperi Rhizoma)*, Ru Xiang* (Frankincense)*,* and *Yan Hu Suo* (Rhizoma Corydalis). One of the major

herbal formulas for treating physical trauma is *Ba Li San* (Eight-Thousandths of Tael Powder) and it also contains *Ru Xiang* (Frankincense), *Mo Yao* (Myrrh), and *Yan Hu Suo* (Rhizoma Corydalis). Similar to *Xing Qi Huo Xue Tang* (Move Qi Invigorate Blood Decoction), *Ba Li San* (Eight-Thousandths of Tael Powder) activates blood circulation to eliminate stasis as well as stimulates the movement of Qi to alleviate pain and swelling. *Ba Li San* (Eight-Thousandths of Tael Powder) is in fact a modification of *Qi Li San* (Seven-Thousandths of a Tael Powder). Yet another classical formula for treating internal and external injuries is *Yao Tong Wan* (Lumbago Pill), which is made up of *Xing Qi Huo Xue Tang* (Move Qi Invigorate Blood Decoction) along with *Ba Li San* (Eight-Thousandths of Tael Powder). *Yao Tong Wan* (Lumbago Pill) has the same function of the herbal formulas that comprise it: activating blood circulation to eliminate stasis and stimulating the movement of Qi to alleviate pain. This formula contains *Ru Xiang* (Frankincense), *Mo Yao* (Myrrh), *Yan Hu Suo* (Rhizoma Corydalis) as well as *Xiang Fu* (Cyperi Rhizoma). One of the primary formulas to treat "blood stasis ailments" is *Huo Xue Hua Yu Tang* (Invigorate Blood Transform Stasis Decoction) which is often used for coronary heart disease, thromboembolism, phlebitis, anemia or dysmenorrhea. It functions by promoting blood circulation to eliminate stasis and relieve pain. This formula pairs *Ru Xiang* (Frankincense) and *Mo Yao* (Myrrh) to increase its blood activating function (Chang, 1999).

Purpose

The purpose of this study is to investigate whether a non-opioid-based herbal formula can reduce acute postoperative pain and analgesic use. Validation of the experimental formula would significantly augment the availability of non-prescription, non-opioid therapy for the treatment of acute pain.

Research Question

1. Can an herbal formula effectively manage acute postoperative pain?
2. Can an herbal formula reduce opioid analgesic consumption postoperatively?

Hypotheses

1. An herbal formula can be safely used pre and postoperatively.
2. An herbal formula can effectively treat acute postoperative pain for low risk outpatient operations.
3. An herbal formula can effectively reduce the need for opioid analgesic use for low risk outpatient operations.

Null Hypotheses

1. An herbal formula cannot be used safely pre and postoperatively.
2. There will be no effect using an herbal formula in the treatment of acute postoperative pain for low risk operations.
3. There will be no change in the need for opioid analgesic use for low risk outpatient operations when using an herbal formula.

Value of Study

If the herbal formula in question can effectively manage acute postoperative pain, then the larger community, both Western and Traditional Chinese Medicine patients, may benefit. The possibility for physicians and surgeons to be able to prescribe a non-addictive, low risk treatment to manage acute postoperative pain may play a significant role in reducing the need for

opioid prescriptions. This may reduce surgeons' inadvertent contribution to the opioid crisis, tempering the risk of opioid addiction. Thousands of lives may be saved if non-opioid based herbal medicine is widely available to the larger community.

Chaper Two: Literature Review

Overview

This chapter will discuss the current research to support the selection of the herbs used in the experimental herbal formula. It will review their application for pain management as well as any known herb drug interactions.

The research information used for this literature review was found on sites such as Pubmed, Google Scholar, and Elsevier Ltd. The key search terms included: Corydalis, *Yan Hu Suo,* Frankincense, Myrrh, Cyperi Rhizoma, Postoperative Pain and Herbal, Fructus Jujubae, *Commiphora myrrha, Boswellia Carteri,* Herb Drug Interaction and Corydalis, Herb Drug Interaction and Frankincense, Herb Drug Interaction and Myrrh, Herb Drug Interaction and Cyperis Rhizoma, Herb Drug Interaction and Fructus Jujubae.

Yan Hu Suo (Rhizoma Corydalis)

Many herbs in the TCM pharmacopeia have analgesic, anti-inflammatory, and/or sedative properties. One of the most widely used herbs for pain and inflammation is *Yan Hu Suo* (Rhizoma Corydalis). Wang et al. (2016) investigated its antinociceptive properties in a rodent model using four standardized pain assays. The use of *Yan Hu Suo* (Rhizoma Corydalis) increased tail flick latency in a dose dependent manner when an acute thermal source was applied. Paw licking after formalin injection was significantly reduced after the administration of *Yan Hu Suo* (Rhizoma Corydalis) in both the early phase corresponding to neurogenic pain and the late phase corresponding to inflammatory pain. *Yan Hu Suo* (Rhizoma Corydalis) was tested on mice who had spinal nerve ligation using the von Frey filament and hotbox assays to measure mechanical allodynia and thermal hyperalgesia. *Yan Hu Suo* (Rhizoma Corydalis) increased paw withdrawal threshold and paw withdrawal latency in these assays. In sum, the

data demonstrate that *Yan Hu Suo* (Rhizoma Corydalis) can suppress nociceptive responses to thermally induced acute pain, chemically induced inflammatory pain, and injury induced neuropathic pain.

Wang et al. (2016) further evaluated two active constituents in *Yan Hu Suo* (Rhizoma Corydalis): dehydrocorybulbine (DHCB) and l-tetrahydropalmitine (l-THP). Five hundred milligrams of *Yan Hu Suo* (Rhizoma Corydalis) contain 1 mg of DHCB and 1 mg of l-THP. The two alkaloids were administered in a mixture of 1 mg each and compared to 500 mg of *Yan Hu Suo* (Rhizoma Corydalis) for their antinociceptive properties. It was found that the mixture of DHCB and l-THP had no effect whereas 500 mg of *Yan Hu Suo* (Rhizoma Corydalis) exhibited significant antinociceptive function. This finding suggests that other components of *Yan Hu Suo* (Rhizoma Corydalis) may be necessary for full antinociceptive activity.

Using the aforementioned assays, Wang et al. (2016) evaluated the potential mechanism of *Yan Hu Suo's* (Rhizoma Corydalis) antinociceptive ability. It was found that the antinociceptive properties of *Yan Hu Suo* (Rhizoma Corydalis) were significantly decreased in dopamine D2 receptor knockout mice. Dopamine D2 receptor is the receptor thought to play an important role in pain and analgesia. It is believed that the antinociceptive effects are mediated at least in part through dopamine D2 receptors in acute and neuropathic pain, but not in inflammatory pain. It was also determined that *Yan Hu Suo* (Rhizoma Corydalis) does not develop antinociceptive tolerance after seven days of daily administration. Also, potential sedative properties were studied in locomotor and rotarod assays and it was not found to significantly affect activity.

Zhang et al. (2014) performed a battery of similar assays to investigate the antinociceptive properties of DHCB. Using the tail flick assay, antinociceptive effects were

found in wild type mice, but not in dopamine D2 receptor knockout mice. The data support the findings of Wang et al. (2016) that the interaction with dopamine D2 receptors are responsible for DHCB's antinociceptive effects. DHCB has a weak affinity to opioid receptors and its antinociceptive function was not affected by naloxone, a non-selective opioid receptor antagonist. Using the formalin assay, DHCB significantly reduced paw licking in the early phase (acute neurogenic pain) and the late phase (inflammatory pain). This effect was dose dependent and effective at a non-sedative dose, which is comparable to that of morphine at high doses. DHCB administered at 10 mg/kg showed no antinociceptive tolerance after seven days when compared to morphine at the same dose. Using the von Frey hair stimulation and hotbox assays on mice who had spinal nerve ligation, DHCB significantly reduced mechanical allodynia and hyperalgesia respectively. These data support that DHCB can suppress the responses to chemically induced, inflammatory derived, and injury induced pain. The results from this study were duplicated using synthetic DHCB.

Yin et al. (2016) investigated dehydrocorydaline (DHC), another alkaloidal component of *Yan Hu Suo* (Rhizoma Corydalis), to determine its anti-inflammatory and antinociceptive function. In an acetic acid induced writhing test, DHC reduced the number of writhings in a dose dependent manner and had a similar effect to morphine and diclofenac sodium. In a formalin paw test, DHC significantly reduced paw licking in the late phase (inflammatory pain) with a similar result as morphine and diclofenac sodium. However, only a high dose (10 mg/kg) of DHC was able to produce an antinociceptive effect in the early phase (neurogenic pain). To determine the possible central antinociceptive mechanism of DHC and its relationship to the opioid system, Yin et al. (2016) tested the effect of naloxone on DHC. The results from the formalin test were completely prevented in the early phase and only partially prevented in the

late phase. DHC reduced paw edema in the formalin paw test in a dose dependent manner and the effect of the high dose (10 mg/kg) was greater than the reference diclofenac sodium group. DHC was not observed to affect locomotor activity, motor responses or produce acute or chronic toxicity. An important observation made by the authors was that the CASP6/TNF-α pathway is directly related to the pain response and triggers the release of proinflammatory cytokines IL-1β, and IL-6. Treatment with DHC was found to down regulate the expression of CASP6, TNF-α, IL-1β, and IL-6 in a dose dependent manner. These data suggest that DHC's antinociceptive mechanism may function centrally via the opioid receptors and peripherally via the inhibition of proinflammatory mediators CASP6, TNF-α, IL-1β, and IL-6 in the spinal cord.

***Xiang Fu* (Cyperi Rhizoma)**

Choi et al. (2012) determined the antinociceptive ability of *Xiang Fu* (Cyperi Rhizoma) and *Yan Hu Suo* (Rhizoma Corydalis) in a chronic constriction injury (CCI)-induced neuropathic pain model in rats. The neuropathic pain behavior was achieved by ligating the sciatic nerve to induce mechanical allodynia and thermal hyperalgesia and was maintained for one month. *Xiang Fu* (Cyperi Rhizoma) or *Yan Hu Suo* (Rhizoma Corydalis) were administered orally and were found to significantly reduce mechanical allodynia in the induction and maintenance phases. They also reduced the pNR1 expression of the spinal dorsal horn suggesting that the antinociceptive function of these herbs might be produced by the mediation of NMDA receptor subunit activity. It is believed that phosphorylation of the NMDA receptor plays an important role in central sensitization, a major component of neuropathic pain. In the thermal heat hyperalgesia model, both *Xiang Fu* (Cyperi Rhizoma) and *Yan Hu Suo* (Rhizoma Corydalis) showed a reduction in the maintenance period, but not in the induction period. This finding

suggests that these herbs may be more effective in treating thermal heat hyperalgesia once the neuropathic pain is established.

Mo Yao (Myrrh) and *Ru Xiang* (Frankincense)

The resins *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) have been used as incense in religious ceremonies since ancient times, however, in TCM they have been used traditionally to treat disease. TCM has been using this powerful herbal combination for thousands of years to synergize the properties of the individual compounds. Cao et al. (2019) reviewed the current research on this herbal pairing to determine that the combination of the two herbs had a more therapeutic effect on disease than each individual herb. Once *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) form a blend, a series of changes take place in their chemical composition. There is either an increase or decrease of the main active ingredients, native chemical components disappear, and new chemical components appear. There is an increase in pharmacodynamics resulting in synergistic anti-inflammation, synergistic analgesic, synergistic anti-cancer, synergistic anti-bacterial, and synergistic blood activation.

Su et al. (2012) investigated the anti-inflammatory activity of combined *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) water extract versus each herbal compound individually in a rodent model. It was found that the *Mo Yao* (Myrrh) and combined *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) water extracts could inhibit formalin induced paw edema. All water extracts were able to suppress carrageenan-induced paw edema, however, the combined *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) water extract was more effective than either individual water extract. Inflammatory cytokine PGE2 was inhibited by all water extracts. To determine analgesic activity, dysmenorrhea was induced by oxytocin. It was found that the combined *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) water extract was most effective to reduce writhing

times and increase the latency period. The *Mo Yao* (Myrrh) water extract reduced the writhing times whereas the *Ru Xiang* (Frankincense) water extract had no effect on either measure. These findings support both *Ru Xiang* (Frankincense) and *Mo Yao* (Myrrh) to have analgesic and anti-inflammatory effects and suggest that the combined *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) herbal pair may be more effective in inflammatory pain than either herb individually.

Hu et al. (2017) investigated the analgesic mechanism behind the herbal combination *Ru Xiang* (Frankincense) and *Mo Yao* (Myrrh) in a neuropathic pain model in mice. Transient receptor potential vanilloid 1 (TRPV1) is believed to play an important role in inflammatory and neuropathic pain and has such been the target of developing drugs to inhibit or block the receptor. However, current research has focused on downregulating the TRPV1 expression as a more effective strategy to modulate pain. Hu et al. (2017) used a water extract of *Ru Xiang* (Frankincense) and *Mo Yao* (Myrrh) to effectively relieve pain in a rodent model. A delayed tail flick response was observed when a heat source was applied and reduced paw licking was noted after capsaicin was injected. In a CCI model, mechanical allodynia and thermal hypersensitivity were induced via spinal nerve ligation. Neuropathic pain was observed by the increase of TRPV1 expression. After a water extract of *Ru Xiang* (Frankincense) and *Mo Yao* (Myrrh) was administered, TRPV1 expression was significantly reduced in a dose dependent manner in real time PCR, Western blot, and immunofluorescense experiments. Also, mechanical withdrawal threshold and thermal withdrawal latency were increased. It was also found that the analgesic effect of a high dose of water of *Ru Xiang* (Frankincense) and *Mo Yao* (Myrrh) had a similar effect to Gabapentin, a commonly used analgesic. In a culture dish, capsaicin was used to activate the dorsal root ganglia of neurons from CCI model mice. A water extract of *Ru Xiang*

(Frankincense) and *Mo Yao* (Myrrh) significantly reduced the ratio and amplitude of the activation of the dorsal root ganglia almost to the same effect as Gabapentin. These findings suggest that the antinociceptive properties of *Ru Xiang* (Frankincense) and *Mo Yao* (Myrrh) are due to its ability to inhibit and downregulate the expression and sensitivity of TRPV1.

Shalaby & Hammouda (2014) investigated the analgesic and anti-inflammatory effects of *Commiphora Molmol* also known as *Mo Yao* (Myrrh) on mice. Using a hot plate test, the reaction time was measured after the administration of *Mo Yao* (Myrrh) and compared to a control group and diclofenac sodium group. *Mo Yao* (Myrrh) significantly increased the reaction time in a dose dependent manner when compared to the control group. Diclofenac sodium also increased the reaction time. Acetic acid was intraperitoneally injected into mice and writhing times were counted. It was found that *Mo Yao* (Myrrh) reduced writhing times, also in a dose dependent manner, when compared to the control group. Aspirin also decreased writhing times. Paw edema was induced by formalin injection and the effect of *Mo Yao* (Myrrh) significantly reduced paw volume (thickness) when compared to a control group. Indomethacin injection also reduced paw volume. The mechanism responsible for *Mo Yao's* (Myrrh) analgesic effect may be due to its bioactive substances that raise pain thresholds by depressing pain receptors centrally in the brain. Or it may be due to the inhibition of the release of prostaglandins, which would explain its anti-inflammatory function. These data confirm the traditional uses of *Mo Yao* (Myrrh) for painful and inflammatory conditions.

Ru Xiang (Frankincense) has been used traditionally in the Middle East for centuries for various health concerns including muscle pain, cough, cold, fever, digestion and stomach pain, arthritis, and even cancer. Al-Harrasi et al. (2014) evaluated the analgesic effects of *Boswellia Sacra* also known as *Ru Xiang* (Frankincense) in a rodent model. Thirteen samples were tested

using the acetic acid induced writhing test and compared to aspirin, chloroform, and control groups in three consecutive phases of 20 minutes. Almost all samples were effective at inhibiting writhing times with comparable results to aspirin. In the formalin assay, most samples had a greater inhibitory effect on the biting and licking response than aspirin and had comparable values to the chloroform groups. The results were significant in both the early and late phases indicating *Ru Xiang* (Frankincense)'s analgesic effect in reducing neurogenic pain (early phase) and inflammatory pain (late phase). Banno et al. (2006) identified the tripertene acids of *Boswellia Carteri* otherwise known as *Ru Xiang* (Frankincense) as the active constituents responsible for the herb's anti-inflammatory function. These data support the traditional use of this herbal medicine for pain relief.

Herb Drug Interactions

An herbal medicine has many different constituents which can exert distinct pharmacological activities. These may place patients at risk if they take herbal remedies concurrently with prescription medications, as there may be adverse drug interactions. Despite public enthusiasm for herbal medicines, our knowledge of adverse events and herbal-drug interaction is incomplete and is largely based on *in vitro* observations, animal studies, and case reports. Among the medicinal herbs in this study, there are case reports of antagonism of warfarin's anticoagulant effect with concomitant use of *Ru Xiang* (Frankincense) (Milic et al., 2014) or *Mo Yao* (Myrrh) (Al Faraj, 2005). Furthermore, an anticoagulant effect has been demonstrated in vitro with *Yan Hu Suo* (Rhizoma Corydalis) (Chang, Yang, Han, Liu, & Yin, 2018). Lastly, a meta-analysis of *Da* Zao (Fructus Jujubae), has indicated no drug interaction or significant adverse events (Yeung et al., 2014).

Rodent studies have revealed various side effects associated with these herbs that have not been reported in human studies. *In vivo* studies have revealed *Xiang Fu* (Cyperi Rhizoma) to have antidiuretic (Uddin, Mondal, Shilpi, & Rahman, 2006) and lactogenic (Badgujar & Bandivdekar, 2015) effects. Systematic reviews have indicated no serious safety and toxicity issues associated with *Ru Xiang* (Frankincense) (Ni et al., 2012) and *Yan Hu Suo* (Rhizoma Corydalis) (Wen, Wu, Ling, & Li, 2007).

The body of evidence in support of herbs for postoperative pain management has largely focused on single herbs rather than herbs used in combination. Despite this evidence and the common use of herbal medications by surgical patients (Pogatzki-Zahn, Segelcke, & Schug, 2014), the study of herbs in postoperative symptom management remains limited and warrants further investigation. For this reason, the current study focuses on evaluating the effectiveness of a combination herbal formula in a postoperative setting and is limited to internal use.

Chapter Three: Method

Design

The chosen study design is that of a prospective, randomized, double-blind, controlled clinical trial in which a combination herbal therapy was administered to half of study participants (experimental arm) and a medically inert substance (microcrystalline cellulose) packaged identical to the herbal therapy was administered to the other half of the participants (control arm). All participants received the standard medical treatment including Acetaminophen, Non-Steroidal Anti-Inflammatory Drug (NSAID) and/or prescription opioid medication.

The Experimental Herbal Formula

The selection of the herbs for this formula was based on their classical use in TCM herbal formulas for pain and traumatic injury as previously discussed in Chapter One. Furthermore, the herb selection is supported by the strong body of literature reviewed in Chapter Two, which documents the analgesic, anti-inflammatory, and antinociceptive properties of these herbs.

The exact composition of the experimental herbal formula used in the current study is as follows:

- *Yan Hu Suo* (Rhizoma Corydalis) 20 g
- *Mo Yao* (Myrrh) 6 g
- *Ru xiang* (Gummi Olibanum*)* 6 g
- *Xiang Fu* (Cyperi Rhizoma*)* 6 g
- *Da Zao* (Fructus Jujubae*)* 3 g

Using the hierarchy of ingredients discussed in Chapter One, *Yan Hu Suo* (Rhizoma Corydalis) can be identified as the Chief herb in this formula. It is considered to be the most

powerful herb for pain relief in the TCM pharmacopeia. This action is consistent with the principal pattern or disease, namely pain, for which the formula was designed. The high dose of 20 grams (standard dose 4.5-12 g) of *Yan Hu Suo* (Rhizoma Corydalis) further indicates it as the Chief herb and potentiates its pain-relieving function. As Deputies, *Mo Yao* (Myrrha) and *Ru Xiang* (Gummi Olibanum*)* reinforce the action of the Chief to relieve pain and are also used for their ability to reduce swelling and promote healing. Additionally, these herbs were selected for their synergistic capacity. A moderate dose of six grams was chosen using the standard range of three to nine grams as a reference. This was in part influenced by the fact that these two herbs can be difficult to digest. The Assistants in this formula are both *Xiang Fu* (Cyperi Rhizoma*)* and *Da Zao* (Fructus Jujubae*). Xiang Fu* (Cyperi Rhizoma*)* supports the function of the Chief and Deputies in its pain-relieving action. Its dose of six grams is on the bottom end of the standard dosage range of six to twelve grams. *Da Zao*'s (Fructus Jujubae*)* role as Assistant is to moderate the harsh properties of the deputies *Mo Yao* (Myrrha) and *Ru Xiang* (Gummi Olibanum*).* Lastly, *Da Zao* (Fructus Jujubae*)* also serves as the Envoy to harmonize and integrate the actions of the other ingredients. For this reason, only a small dose of three grams (standard dose 10-30 grams) was used. The participant daily dose of eight grams was selected according to an average individual weighing 200 lbs.

The herbal formula and placebo were purchased from Sun Ten Laboratories in Irvine, CA. Sun Ten sources their herbs from Taiwan and uses rigorous testing measures to ensure their safety and quality. The individual herbs were decocted, extracted, and concentrated to be sprayed on to vehicle carriers such as potato or corn starch. The herbal formula was custom made using the granulated herbs and encapsulated into 500 mg gelatin capsules. The placebo consisted of encapsulated microcrystalline cellulose.

Human Subjects Ethical Considerations

This study was conducted following the current Federal guidelines for the ethical treatment of human subjects. The proposal for the current study was reviewed by the Yo San University Institutional Review Board (IRB). A copy of the IRB approval letter is included in Appendix D.

Sample

The 48 participants were recruited to the study as surgical candidates from the outpatient offices of Dr. Turek and Dr. Towfigh. The specific inclusion criteria included adults, aged 21-75 years, fluent in English, who qualified for common low risk outpatient operations involving the male reproductive system or abdominal wall and pelvic hernias. These operations included vasectomy, vasectomy reversal, varicocele repair, sperm retrieval, inguinal hernia repair, umbilical hernia repair, revisional hernia repair, mesh removal, neurectomy, or inguinal and scrotal neurolysis procedures. Forty participants had procedures related to the male reproductive system and eight participants procedures involving hernia repair.

The specific exclusion criteria included: patients with a history of chronic pain outside of the intended surgical anatomical area, patients with a history of addiction and medication abuse, patients under the care of a Pain Management specialist and requiring complex regimen or opioid analgesics, patients who were not compliant with screening and consent procedures, patients allergic to acetaminophen, NSAID, and/or opioid medications, corn and/or potato starch (the carrier for the experimental formula), and/or microcrystalline cellulose (the control), and pregnant females were also excluded from the study, as the combination herbal regimen has yet to be studied for its safety in non-pregnant subjects.

Instrument

The instrument used to score the analgesic consumption and the pain experienced post-operatively by the participant was the Pain Pill Score Sheet with Visual Analog Pain Scale. See Appendix B. The pain aspect of the Pain Pill Score Sheet included pain frequency, duration, and intensity as assessed by the validated Wong-Baker 11-point pain rating scale (Aziato, Dedey, Marfo, Asamani, & Clegg-Lamptey, 2015). The Pain Pill Score Sheet assessed the impact of pain on subject's quality of life (e.g., normal activities and sleep) as assessed by a shortened version of the validated Brief Pain Inventory Short Form (Keller et al., 2004). Additionally, participants logged their daily consumption of analgesics including type of analgesic, quantity, and dose on Pain Pill Score Sheet.

Data Collection Procedures

Once participants were screened to verify that they met the inclusion and exclusion criteria, they were consented and reviewed instructions regarding study participation and participant rights. This process was completed in the office by the surgeon, study coordinator, or primary investigator. Subjects enrolled in the study were placed in either the control arm (placebo offered) or the experimental arm (herbals offered) in a blind, randomized, prospective manner. Subjects in both groups followed the same instructions taking the herbal regimen (experimental arm) or placebo regimen (control arm). The bottles containing the herbal and control regimens were labeled exactly the same and contained 136 capsules. Subjects took eight capsules twice daily for the three days prior to and five days following surgery. No capsules were taken on the morning of the surgery, but then eight capsules were resumed the evening of the surgery. Both arms of the study received a physician dependent standardized analgesic

treatment: Acetaminophen, NSAID and prescription opioid medications. Participants undergoing hernia surgery performed by Dr. Towfigh were prescribed Naproxen 500 mg two times daily, Tylenol 500 mg two to three times daily, and Tramadol 50 mg for breakthrough pain as needed. Those participants undergoing urological surgeries conducted by Dr. Turek were prescribed Tylenol 3, which consists of Acetaminophen 300 mg and Codeine 30 mg, every four hours. Vasectomy procedures were prescribed a total of 12 tablets, varicocele repair 16 tablets, and vasectomy reversal 20 tablets. Participants were asked to complete the Pain Pill Score Sheet beginning the evening of the operation and then for five days thereafter for a total of six daily Pain Pill Score Sheets.

Phone calls were made to the subjects by the primary investigator and/or study coordinator at three days, two days, and once day before the scheduled procedure. The calls served to remind the subject to take their capsule regimen and to clarify any questions or concerns. For the day of the procedure and for each of the following five days, participants were reminded via text messages from the study coordinator or primary investigator to take their capsules and to complete the Pain Pill Score Sheet.

Double blinding of the contents of the pill bottles (i.e., placebo or herbal) was achieved by labeling each pill bottle a number and randomly assigning (randomlists.com) that number to a subject's ID. The bottle number, contents, and subject ID were recorded in a file that was not accessed until after the study's completion. During the study, investigators only knew the pill bottle number assigned to each subject. Drs. Towfigh and Turek provided a monthly adverse events report to the primary investigator.

Data Analysis

A quantitative inferential statistical analysis program was used to analyze the data. Descriptive statistics and simple parabolic comparative statistics including means, standard deviations, skewness, Mann Whitney U test, and Pearson chi-square analyses were applied to assess the following outcomes:

Primary outcome: the number of total analgesic pills used postoperatively.

Secondary outcome: the number of opioid pain pills used postoperatively.

Tertiary outcome: Trend of pain scores on each of five days after surgery. This outcome measure will assess subjective pain control rather than objective analgesic use.

The following instruments were used to assess these outcomes:

1. A Pain Pill Score Sheet that was provided to the patient and completed daily for 5 days after surgery (6 total pain pill score sheets including evening of surgery). The score sheet includes both opioid and non-opioid pain medications. This score sheet measures the primary and secondary outcome: total analgesic consumption and opioid analgesic consumption, respectively.
2. A validated analog pain scale question integrated in the Pain Pill Score Sheet that was provided to the patient and completed daily for 5 days after surgery (6 total pain journals including evening of surgery). This pain scale question measures the tertiary outcome: trend in patient's subjective pain scores postoperatively.

Chapter 4: Results

Data Overview

The goal of this study was to assess if a non-opioid-based herbal formula can reduce acute postoperative pain and opioid analgesic use. The clinical trial hypotheses were that an herbal formula could be used safely pre and postoperatively, could effectively treat acute postoperative pain, and could reduce opioid analgesic consumption in low risk outpatient surgeries. The accompanying null hypotheses stated that an herbal formula cannot be used safely pre and postoperatively, there will be no effect using an herbal formula in the treatment of acute postoperative pain, and there will be no change in the need for opioid analgesic use for low risk outpatient operations when using an herbal formula.

Prior to conducting parametric analyses to test the research questions, the normality assumption was assessed for the continuous study measures using *z*-scores formed by dividing skewness by the standard error of skewness. A *z*-score within +/- 3.29 is indicative of a normal distribution (West, Finch, & Curran, 1995). The results are presented in Table 1. The distributions of half of the continuous measures were skewed, which violated the normality assumption underlying parametric comparative statistics. Therefore, a decision was made to use non-parametric methods to compare the Experimental and Control groups. It was decided to exclude data collected from the day of the surgery as participants were still experiencing the effects of operative medication. Thus, only the data from postoperative days one through five were used in the analysis.

Pain scores and level of interference with daily activity were measured on an eleven-point scale ranging from 0 to 10. As shown in Table 1, the mean total pain scores and interference with daily activity decreased with time from postoperative (PO) day one to PO day

five. For all the data from PO days one through five, the standard deviation was equal to or greater than the mean indicating that there was a high level of variation. The data were skewed for PO days four and five for both pain scores and interference with daily activity. Total pain scores and pain pills used were also skewed. Since the data were lumped at one side or another of the distribution curve, it reflects that participants either took a lot or very few pain pills. The mean total interference with daily activity score was approximately equal to the standard deviation, however the data were not skewed. This finding reflects that there were equally as many participants whose pain interfered with their daily activity as those with which it did not interfere.

Table 1
Summary Statistics

	N	*Mean*	*SD*	*Skewness*	*SE*	*z*	
Pain Scores							
PO Day1	48	2.44	2.29	0.91	0.34	2.66	
PO Day2	47	1.98	1.88	1.12	0.35	3.21	
PO Day3	44	1.59	1.58	1.14	0.36	3.18	
PO Day4	45	1.33	1.48	1.60	0.35	4.53	*
PO Day5	45	1.33	1.57	1.57	0.35	4.43	*
Total Pain Score	48	9.52	9.29	1.42	0.34	4.13	*
Total Number of Pain Pills	48	3.92	5.77	1.78	0.34	5.20	*
Interference with Daily Activity							
PO Day1	48	3.27	3.05	0.68	0.34	1.99	
PO Day2	46	2.76	2.89	0.94	0.35	2.69	
PO Day3	44	2.02	2.24	1.08	0.36	3.03	
PO Day4	45	1.89	2.16	1.45	0.35	4.09	*
PO Day5	45	1.69	2.12	1.37	0.35	3.88	*
Total Activity Score	48	12.47	12.78	0.99	0.34	2.88	

* skewed distribution

Pain Scores

Pain scores for each postoperative (PO) day, and the Total, summed across the five days were compared between the Experimental and Control groups in Table 2. (Missing pain scores were estimated using mean substitution.) Mann-Whitney *U* tests were used to compare the groups. There was no significant difference in pain scores for any of the PO days. It appeared that there was a progression of lessening of pain that is more pronounced in the Experimental group. However, due to the small sample size and the skewness, it was not possible to analyze the progression.

Table 2
Experimental versus Control on pain scores

	Experimental			Control				
Pain Scores	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*	*Mann-Whitney U*	*p*
PO Day 1	24	2.67	2.14	24	2.21	2.45	233	0.248
PO Day 2	24	2.04	2.01	23	1.91	1.78	272	0.931
PO Day 3	21	1.43	1.29	23	1.74	1.82	230	0.781
PO Day 4	22	1.05	1.09	23	1.61	1.75	212	0.332
PO Day 5	22	1.00	1.23	23	1.65	1.80	196	0.176
Total (Sum)	24	9.20	8.92	24	9.83	9.83	286	0.967

Pain Pill Use

Incidences of any pain pill use for each postoperative (PO) day, and any use across the five days were compared between the Experimental and Control groups are shown in Table 3. Pearson chi-square analyses were used to compare the groups. No significant effect was found, although it seemed as though the Experimental group used more pain pills. Both groups displayed a decreasing trend in the number of pain pills used, but this trend was unable to be tested due to the small sample size of each group.

Table 3
Experimental versus Control on incidence of any pain pill use

	Experimental				Control					
Any Pain	Yes		No		Yes		No			
Pills Used	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	$\chi 2$	*p*
PO Day 1	15	62.5%	9	37.5%	11	45.8%	13	54.2%	1.34	0.247
PO Day 2	11	45.8%	13	54.2%	8	33.3%	16	66.7%	0.78	0.376
PO Day 3	6	25.0%	18	75.0%	5	20.8%	19	79.2%	0.12	0.731
PO Day 4	5	20.8%	19	79.2%	6	25.0%	18	75.0%	0.12	0.731
PO Day 5	4	16.7%	20	83.3%	5	20.8%	19	79.2%	*	1.000
Overall	15	62.5%	9	37.5%	12	50.0%	12	50.0%	0.76	0.383

* Fisher's exact test (minimum expected cell size < 5)

Table 4 shows the number of pain pills taken across five postoperative (PO) days was compared between the Experimental and Control groups (Note that the 21 patients who did not take any pain pills were scored zero for this measure.) A Mann-Whitney *U* test was used to compare the groups and no statistical significance was determined. It appeared that the Experimental group was taking more pain pills, but this finding was also not statistically significant. Participants used a wide variety of NSAIDs including Acetaminophen, Ibuprofen, Naproxen, and Tylenol with strengths ranging from 162 mg to 800 mg. One pain pill was calculated at 500 mg for the purpose of analyzing the data. However, opiates were not standardized by strength such that one Tramadol 50 mg tablet was counted equal to one Oxycodone of variable dose.

Table 4
Experimental versus Control on number of pain pills taken across five post-operative days

	Experimental			Control				
	N	*Mean*	*SD*	*N*	*Mean*	*SD*	*Mann-Whitney U*	*p*
Number of Pain Pills	24	4.29	6.08	24	3.54	5.55	286	0.967

Incidences of opiate pain pill use for each postoperative (PO) day were compared between the Experimental and Control groups are shown in Table 5. Pearson chi-square analyses were used to compare the groups. Postoperative day one revealed that the Experimental group 45.8% used more opiates than the Control group 12.5%, this effect was statistically significant.

Table 5
Experimental versus Control on incidence of any opiate pill use

	Experimental				Control					
Any Opiate Pills	Yes		No		Yes		No			
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*χ2*	*p*
PO Day 1	11	45.8%	13	54.2%	3	12.5%	21	87.5%	6.45	0.011
PO Day 2	6	25.0%	18	75.0%	2	8.7%	21	91.3%	*	0.245
PO Day 3	5	23.8%	16	76.2%	1	4.3%	22	95.7%	*	0.088
PO Day 4	3	13.6%	19	86.4%	0	0.0%	23	100.0%	*	0.109
PO Day 5	1	4.5%	21	95.5%	1	4.3%	22	95.7%	*	1.000

* Fisher's exact test (minimum expected cell size < 5)

Interference with Daily Activity

Interference with daily activity scores for each postoperative (PO) day, and the Total, summed across the five days were compared between the Experimental and Control groups in Table 6. (Missing pain scores were estimated using mean substitution.) Mann-Whitney *U* tests were used to compare the groups. No statistical significance was found between the groups. For all PO days and the Total, the standard deviation was equal to or greater than the mean value of the interference with daily activity score. This high level of variation shows that some participants' daily activity was affected by their pain and others were not affected.

Table 6
Experimental versus Control on interference with daily activity scores

Interference with Daily Activity	Experimental			Control				
	N	*Mean*	*SD*	*N*	*Mean*	*SD*	*Mann-Whitney U*	*p*
PO Day1	24	3.38	3.16	24	3.17	3.00	274.5	0.778
PO Day2	23	3.00	3.22	23	2.52	2.57	247	0.696
PO Day3	21	2.14	2.31	23	1.91	2.21	222.5	0.647
PO Day4	22	2.09	2.35	23	1.70	1.99	228	0.560
PO Day5	22	1.64	2.30	23	1.74	1.98	235	0.669
Total (Sum)	24	12.90	13.68	24	12.04	12.10	284	0.934

Safety

It was determined that the experimental herbal formula is safe for use as there were no serious adverse events. Of 50 enrolled participants, five participants reported incidences of bloating or vomiting and withdrew from the study. Data collected prior to withdrawal of the study were used in the statistical analysis. The current study had a 10% withdrawal rate due to adverse events.

Chapter 5: Discussion

Summary of Findings

This double blind prospective randomized clinical trial was conducted to determine if a non-opioid-based herbal formula can reduce acute postoperative pain and opioid analgesic use. The researcher's hypotheses were that an herbal formula could be used safely pre and postoperatively, could effectively treat acute postoperative pain, and could reduce opioid analgesic consumption in low risk outpatient surgeries. The accompanying null hypotheses stated that an herbal formula cannot be used safely pre and postoperatively, there will be no effect using an herbal formula in the treatment of acute postoperative pain, and there will be no change in the need for opioid analgesic use for low risk outpatient operations when using an herbal formula. The statistical analyses revealed that the herbal formula was safe to use pre and postoperatively, however, it was not found to effectively treat acute postoperative pain nor lower opioid analgesic consumption.

Implications for Theory

The current study does not support the literature cited in Chapter Two: Review of the Literature, which demonstrates the potent analgesic, antinociceptive, and anti-inflammatory functions of the TCM herbs used in the experimental formula. Wang et al. (2016) found that *Yan Hu Suo* (Rhizoma Corydalis) was comparable to morphine in treating neurogenic and inflammatory pain. Hu et al. (2017) found *Mo Yao* (Myrrh) and *Ru Xiang* (Frankincense) to be as effective as Gabapentin in treating pain. Additionally, Al-Harrasi et al. (2014) determined that *Ru Xiang* (Frankincense) was better than aspirin and comparable to chloroform in treating neurogenic and inflammatory pain. One must take into account that these experiments were all

performed in rodent models, where all variables can easily be controlled. Theoretically, the formula in question should have been capable of reproducing these analgesic, antinociceptive, and anti-inflammatory effects. Since the current study was unable to reduce pain pill and opioid analgesic consumption with the experimental herbal formula, the various limitations must be examined in order to overcome these obstacles in future research.

Implications for Practice

Although the experimental herbal formula did not decrease pain pill and opioid analgesic use or effectively treat postoperative pain treatment, it was determined to be safe for pre and postoperative use. TCM practitioners can safely prescribe this formula for their patients undergoing surgery and modify as needed to reflect the patient's differential diagnosis, a limitation which will be discussed in the following subsection. In regards to Western Medicine, this herbal formula will need to be researched further with adequate modifications to address the limitations of the current study before it would be able to be widely used in practice.

Limitations of the Current Study

The great disparity and skewness in pain scores and pain pill use may be in part due to the wide variety of surgery types which were included in the current study. Dr. Towfigh performed abdominal, pelvic, inguinal, and umbilical hernia surgeries exclusively, which when compared to the urological surgeries performed by Dr. Turek such as vasectomy, vasectomy reversal, sperm retrieval, and varicocele repair are more invasive and potentially more painful. Another reason may be the diversity in the types of medication used by participants. Each surgeon used a separate medication protocol. Dr. Towfigh prescribed NSAIDs and Tramadol

was only indicated for breakthrough pain. Whereas Dr. Turek prescribed Tylenol 3 (with Codeine) yet some of his patients took Percocet and Oxycodone. It was not possible to account for the difference in opiate potency across participants in the data analysis. Furthermore, some participants self-medicated using CBD and cannabis, which was a factor that was unable to be controlled.

Another possible limitation is participant compliance. Participants took eight capsules twice daily for eight days and only once on the day of surgery, totaling 136 capsules. The large quantity of capsules may have been difficult for participants to take. Also, participants may have forgotten doses, which could decrease the herbal formula's analgesic potential. Herbal medicine differs from pharmaceuticals in that it must first build up in the blood to have an effect. For this reason, participants were instructed to start the formula in the preoperative phase as a form of preemptive analgesia. Participants who attempted to make up missed doses may have taken them too close together or even taken all 16 capsules at once. This could lead to adverse events such as bloating, nausea or vomiting. Adverse events were also reported in the Control group, which could indicate that the experimental herbal formula may not have been the cause, but the quantity of capsules.

In TCM, an individual differential diagnosis is made by the practitioner according to their tongue presentation, pulse, and medical history and is used to create a treatment plan or herbal formula specifically tailored to their case presentation. For the purpose of this study, one herbal formula with a standardized dose of eight grams was created for a person weighing 200 lbs. It was not possible to take into consideration individual differences such as sex, age, weight, digestion, medications, etc. For this reason, the experimental herbal formula dose could not be customized for a female participant weighing 110 lbs. or a male participant weighing 240 lbs. In

TCM, the female would be prescribed a lower dose than her male counterpart. This phenomenon could explain why two female participants withdrew from the study due to vomiting. The dose may have been too strong. On the other hand, this could account for a male participant weighing over 200 lbs. who needed to take more pain pills because the prescribed herbal dose was not strong enough to have an analgesic effect.

Subjective pain measures played a role in the large variation of pain scores and pain pill use. For example, one participant scored 0/10 on the eleven-point pain scale after a varicocele repair. Another participant scored 6/10 for the same procedure. Neither participant took any pain pills. Conversely, another participant took Oxycodone for 5/10 pain after sperm retrieval. Individual factors which determine pain tolerance could not be accounted for in the current study. These factors may be partially responsible for the Control group taking less opiates than the Experimental group. Additionally, the placebo effect may have contributed to this effect.

Recommendations for Future Research

Given the many limitations of the current study, future research should be conducted using a larger sample size with only one type of surgery such as hernia or vasectomy. Participants should all be prescribed the same medication protocol with self-medication of other substances discouraged. Additionally, the experimental herbal formula should be dosed according to the participant's weight and when possible individual factors such as constitution, age, digestion, medications should be taken into consideration. In order to increase patient compliance, an alternate form of the herbal formula administration should be developed such as an alcohol or glycerin-based tincture. A concentrated liquid version of the formula would eliminate the need to swallow numerous capsules. Also concocting all of the raw herbs together,

as opposed to cooking the raw herbs separately and compounding the granules, may increase the herbal synergy of the formula. When the herbs are cooked together the active ingredients can interact with one another to form new and potentially more potent active constituents.

Conclusion

The current study demonstrated that a non-opioid based herbal formula was able to be safely used pre and postoperatively. However, it was not able to effectively treat acute postoperative pain or decrease pain pill and opioid analgesic consumption. Further research using the experimental formula could be promising as the safety has been established and the effectiveness of the herbs has been documented in numerous studies. As the opioid crisis continues to be a national epidemic, it is the primary investigator's hope that the current study will engender more research using non-opioid-based herbal formulas for the treatment of acute postoperative pain. There is a vast history and wealth of medicinal power in TCM pharmacopeia, the challenge lies in harnessing its potential and packaging it in such a way that it can be easily integrated into mainstream Western Medicine.

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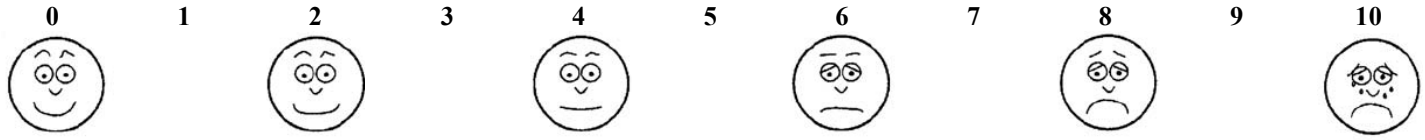
Appendix A: Pain Pill Score Sheet

Subject ID #: _____ **Today's date_____** **Date of Operation:_____**

1. **Please circle the number on a scale from 0 to 10 that best describes your <u>average pain over the past 24 hours</u>:**



2. **If you've taken any pain medications <u>in the past 24 hours</u>, please indicate the type, dosage, and quantity:**

Pain Medication Type	*Dose (mg)*	*# pills*
Acetaminophen (e.g., Tylenol):		
Ibuprofen, Naproxen (e.g., Advil, Motrin, Aleve):		
Tramadol (Ultram):		
Codeine (e.g., Tylenol with codeine):		
Hydrocodone (e.g., Norco, Vicodin):		
Oxycodone (e.g., Percocet):		
Other:		

3. **Circle the % that describes how much pain relief these medications provided in the <u>last 24 hours</u>:**

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

No relief **Complete relief**

4. **Please circle the number that best describes how, <u>during the past 24 hours</u>, pain has <u>interfered</u> with your:**

a. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

b. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

c. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

d. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										**Completely interferes**

REMINDER: PLEASE TAKE YOUR CAPSULES TONIGHT AND TOMORROW MORNING

Appendix B: Informed Consent

TITLE: NON-OPIOID, HERBAL FORMULA FOR POSTOPERATIVE PAIN

SPONSORS: THE TUREK CLINICS; BEVERLY HILLS HERNIA CENTER

RESEARCH TEAM AND CONTACT INFORMATION:

Primary Investigator: Kristel Hart, L.Ac., Dipl. OM	khart.student@yosan.edu	(310)-869-0712
Study Coordinator: Charles Herndon, BA, BS	charles.herndon@ucla.edu	(415)-515-8255
Study Coordinator: Isabel Capati RN, BSN.	info@beverlyhillsherniacenter.com	(310)-358-5020
Co-Investigator: Shirin Towfigh, MD		
Co-Investigator: Paul J. Turek, MD		

WHAT IS THE PURPOSE OF THE STUDY?

This study evaluates the efficacy of a non-opioid based herbal formula for the management of postoperative pain. You are being asked to participate in the study because your surgeon has determined that you are a suitable candidate. Your participation in the study is entirely optional. If you choose not to participate in the study, your surgery will proceed as planned, however, no data will be collected on you for the purpose of the study nor will your surgeon provide you with research-related treatment.

This study will enroll up to 150 people.

WHAT WILL HAPPEN DURING THE STUDY?

This section provides an overview of what will happen during your participation in this study. Please consider this information alongside the flowchart that is provided in Appendix A.

Screening and Data Collection:

If you choose to participate in this study, you will go through an initial screening process in order to determine your eligibility. If you meet all of the criteria and agree to participate, you will be enrolled in the study. You will be asked for some information, including your date of birth, gender, height, weight, current pain medications, current medical problems, and overall health. You will also be asked for your phone number and email so that the study coordinator can reach you for telephone check-ins and any other information necessary for the study.

Once this information is collected, you will be provided with a numbered bottle containing capsules that are composed of either the herbal formulation or an inactive formulation. Neither you nor the research team will know the composition of the capsules that you have been provided. The composition of the numbered bottles assigned to participants will only be learned by the research team upon the completion of the study. You will be asked to take the capsules twice daily, beginning three days before the date of your operation and continuing for five days afterward. You will not take the capsules on the morning of the day of your operation, but will start taking the capsules the evening of the day of your operation. In conjunction with the capsule regimen, you will be provided with a conventional pain medication prescription to aid (if necessary) in postoperative pain management.

Pain Journal:

You will be asked to complete a daily pain journal beginning the evening of the day of your operation and continuing daily for five days after your operation. This questionnaire asks you to rate any physical pain related to your operation that you may experience, as well as how that pain affects your general activity, mood, sleep, and enjoyment of life. If you took any pain medication (aside from the capsules) to aid in your pain management that day, you will record the type and quantity of that medication daily. When the last pain journal is completed, you will be asked to return them all to your surgeon's office.

Phone Calls/Text Messages:

The study coordinator will reach you by phone on each of the three days before your operation. Then you will receive a text message on the day of your operation and daily for the next five days. These communications are made to address any questions or concerns you have about the research study. The conversation also confirms with the study coordinator that you are completing the pain journal as well as taking the herbal formulation as scheduled. These conversations may take up to 5 minutes to complete.

WHAT ARE THE RISKS AND BENEFITS?

This section discusses possible risks and discomforts we anticipate you may experience related to the study.

Data Collection:

This study will need to collect your private health information as well as your responses to the daily pain journal. We do not expect that this data collection will increase any risk to you. The only foreseeable risk associated with data collection is unauthorized access to your personal health and contact information; however, the research team will make every effort to minimize this risk. For instance, the pain journal will be labeled with a unique study number that will link your identity so that only the research team can identify you.

Treatment:

Your participation in this study will not affect the method or type of surgery that you need. Additionally, we do not expect the herbal formulation to lead to any complications before, during, or after your surgical operation. The safety of the study's herbs has been confirmed by several clinical trials and toxicity studies. There are, however, case reports and laboratory findings suggesting that the study's herbal regimen may increase the risk of bleeding during surgery and/or could cause nausea, stomach upset or loose stools. Even though these cases are exceedingly rare, the study asks that you take precaution and do not take the herbal formulation on the morning of the day of your operation.

ARE THERE ANY BENEFITS IN TAKING PART IN THE STUDY?

Taking part in this study is completely voluntary and compensation will not be provided. You may potentially benefit from decreased postoperative pain as well as decreased reliance on conventional pain medications for pain management. Your participation in this study may indirectly benefit future patients by aiding in the development of non-opioid alternatives in the treatment of acute postoperative pain.

WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the research team without your consent for any reason, including:

- The study has been stopped or suspended
- Funding for the study is reduced or withdrawn
- You do not consent to continue in the study after being told of changes in protocol that may affect you
- You do not follow the study operations
- You become aware, either intentionally or inadvertently, of the composition of your provided tablets

If you decide to participate in the study, you will be asked to adhere to all instructions issued by the research team. These include:

- Reporting any medications or medical problems
- Daily completion of the pain journal and returning the completed pain journal to your surgeon's office
- Taking the herbal formulation according to schedule
- Completing telephone check-ins to confirm that you are completing the regimen and journal

WHO DO I ASK TO LEARN MORE?

For questions concerning the study's design and protocol as well as your role in the study, you may reach the primary investigator or study coordinators whose contact information is provided on page one of this form. For questions on your rights as a participant, please contact the Yo San University of Traditional Chinese Medicine Institutional Review Board at irb@yosan.edu.

Statement of Consent: I have read the above information and have received answers to any questions I asked. I consent to take part in the study.

Signature by the Participant:

Printed Name of Participant	Signature of Participant	Date

Signature by the Researcher Obtaining Consent:

I attest that all elements have been discussed fully in non-technical terms with the subject. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Printed Name of Researcher	Signature of Researcher	Date

This consent form will be kept by the research team for at least three years beyond the end of the study. You will be provided a copy of the consent form for your own records.

Appendix A

Flowchart of Study: Schedule of when the herbal formula is taken as well as when the pain journal and phone/text are to be completed.

Pre-Operative Appointment				
3 Days Before Surgery	☐Take Capsules AM	☐Take Capsules PM		☐Phone Call
2 Days Before Surgery	☐Take Capsules AM	☐Take Capsules PM		☐Phone Call
1 Day Before Surgery	☐Take Capsules AM	☐Take Capsules PM		☐Phone Call
Day of Surgery	■NO CAPSULES AM	☐Take Capsules PM	☐Complete Pain Journal	☐Text msg
1 Day After Surgery	☐Take Capsules AM	☐Take Capsules PM	☐Complete Pain Journal	☐Text msg
2 Days After Surgery	☐Take Capsules AM	☐Take Capsules PM	☐Complete Pain Journal	☐Text msg
3 Days After Surgery	☐Take Capsules AM	☐Take Capsules PM	☐Complete Pain Journal	☐Text msg
4 Days After Surgery	☐Take Capsules AM	☐Take Capsules PM	☐Complete Pain Journal	☐Text msg
5 Days After Surgery	☐Take Capsules AM	☐Take Capsules PM	☐Complete Pain Journal	☐Text msg

Appendix C: HIPAA Authorization Form

AUTHORIZATION TO USE & DISCLOSE IDENTIFIABLE HEALTH INFORMATION FOR A RESEARCH STUDY

This authorization agreement gives permission to the research team to use or disclose identifiable health information in the research study on the "Development of an Effective Herbal, Non-Opioid-Based Therapy to Treat Acute Postoperative Pain". The research team includes Kristel Hart, L.Ac., Dipl. OM, Paul J. Turek, MD, Shirin Towfigh, MD, Charles Herndon, BS, and Isabel Capati RN, BSN.

The identifiable health information used in this research study includes your name, gender, date of birth, date of procedure, type of procedure, list of current medications, surgical treatment record, as well as your responses to the pain journal.

The research team is required by law to protect your health information. The research team will only use & disclose the health information that is minimally necessary to conduct the research study. In order to maintain the integrity of the research process as well as to avoid potential biases in its analysis & publication, you may not have access to the health information developed as part of the research study. Your identifiable health information will be made anonymous prior to this research's publication. After it is made anonymous, your health information is not subject to this authorization and may be used by the research team for purpose of publication.

Your health information may be shared with the Institutional Review Board of Yo San University of Traditional Chinese Medicine as well as other persons who are not part of the research team. The research team will make reasonable efforts to ensure that recipients of your health information maintain the confidentiality of your health information and that only the minimally necessary level of information is shared. Persons outside of the research team could, in very rare cases, reveal your health information for purposes related to the research study. This would be an unauthorized and illegal disclosure of your information. The research team does not expect this to happen. Moreover, California law prohibits such unauthorized disclosure of health information.

This authorization does not have an end date; however, you have the right to refuse or revoke this authorization at any time. If you choose to refuse or revoke the authorization, you will not be allowed to participate in the research study. However, standard care treatment by your physician will still be made available to you. If you choose to revoke this authorization, the research team will only have access to the health information that had already been gathered and developed up until the time you choose to revoke the authorization. In order to revoke this authorization, you must write to your physician's address:

Paul J. Turek, M.D.
55 Francisco St.
San Francisco, CA 94133

Shirin Towfigh, M.D.
450 N. Roxbury Dr. Ste. 224
Beverly Hills, CA 90210

The research team is required by law to protect your health information. By signing below, you authorize the use and disclosure of your health information in connection with the research study described above.

Signature by the Participant:

Printed Name of Participant | Signature of Participant | Date

Signature by the Researcher Obtaining Consent

I attest that all elements have been discussed fully in non-technical terms with the subject. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Printed Name of Researcher	Signature of Researcher	Date

This consent form will be kept by the research team for at least three years beyond the end of the study. You will be provided a copy of the consent form for your own records.

Appendix D: Institutional Review Board Approval Letter

YO SAN UNIVERSITY
OF TRADITIONAL CHINESE MEDICINE

January 30, 2019

Kristel Hart
12340 Rochester Ave, #120
Los Angeles, CA 90025

Dear Kristel,
Your research proposal has been approved, with no additional recommendations effective through March 31, 2020.
Should there be any significant changes that need to be made which would alter the research procedures that you have explained in your proposal, please consult with the IRB coordinator prior to making those changes.

Sincerely,

Farshid T. Namin

Farshid T Namin
IRB Coordinator