Contents of the talk

- Chinese Herbal medicine for pain – History and theory
- Treatment of pain with Chinese herbs – some examples
- Pharmacological basis of Chinese herbs for pain
- Is it effective? – systematic review of published literature
Chinese Herbal medicine for pain – History and theory

- CM has long been used for pain management.

**The Inner Classic of the Yellow Emperor 黃帝內經**

- devotes an entire chapter to the studies of pain, 黃帝內經－舉痛論
- lays the theoretical foundation for the etiology, pathogenesis and treatment strategies for pain.

How CM views pain – Basic concepts

Blockage of meridians causes pain; pain is caused by impediment of circulation of qi and blood 不通則痛

*Wind, cold, dampness, heat, qi stagnation, blood stasis, Phlegm turbidity can cause blockage of meridian and qi/blood circulation.*

Deficiency of vital substances (nutrients) also causes pain 不榮則痛
Management of pain – CM perspective

- To expel the pathogenic factors that cause the blockage of meridians.
  - Expelling wind,
  - Dispelling cold,
  - Transforming dampness
  - Clearing heat,
  - Dissolving food stagnation
  - Regulating qi stagnation
  - Invigorating blood circulation
  - Transforming phlegm turbidity.

- Nourishing yin essence
- Warming yang
- Supplementing qi
- Tonifying blood

Pain

To supplement the deficiency of vital substances.

Chinese herbs with analgesic effects

- Over 300 Chinese herbs are known to have analgesic effects for various pains.
- According to their functions and indications in CM, they are broadly categorized into the following types:
• Exterior-resolving analgesic herbs: 解表止痛藥: 白芷 細辛 羌活.
• Wind-dampness expelling analgesic herbs: 祛風濕止痛藥: 威靈仙 獨活 秦艽.
• Heat-clearing analgesic herbs: 清熱止痛藥: 山豆根 射干 馬勃.
• Blood invigorating & stasis removing analgesic herbs: 活血祛瘀止痛藥: 延胡索 乳香 没藥 三七.
• Qi-regulating analgesic herbs: 行氣止痛藥: 木香 香附 烏藥.
• Interior-warming analgesic herbs: 溫里止痛藥: 高良姜 吳茱萸.
• Anesthesiac analgesic herbs: 麻醉止痛藥: 川烏 草烏 祖師麻 曼陀羅.
• Other analgesic herbs: 其他止痛藥: 雎粟殼.

Routes of administration of CM

• Oral (decoction, tincture, pills, tablets, capsules, granule, powder)
• Topical (paste, plaster, balm, ointment, spray)
• Injection (i.v. and i.m.)
• Steaming and bathing.
Treatment of pain with Chinese herbs – some examples


Types of pain and baseline data

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer pain</td>
<td>16</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>Post-stroke limb pain</td>
<td>11</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Rheumatoid arthritis pain</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Soft tissue pain</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Osteoarthritis pain</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Pain with no clear cause</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**Methods:**

- Double-blind (patients, researcher blinded)
- Block randomization (quasi-)
- Preparation of Bing-Chan tincture:
  - Composition: 冰片 蟾蜍 血竭 紅花 乳香 沒藥 田七. The above materia medica were ground to powders and then soaked in white wine for 7 days. The alcoholic extract was used for treatment.
- Application: the extract was applied 4-5 times daily to the pain area. Other analgesics suspended.
- Duration: 7 days as a course of treatment.
- Control treatment: 紅花 tincture.

**Treatment evaluation:**

- VAS (Developed by Zhongshan Hospital, Shanghai Medical University)
  - significantly effective 顯效 – reduction 40-100;
  - effective 有效 – reduction 10-40;
  - Ineffective 無效 – reduction <10, or need other analgesics;
  - worsened 惡化 – increase > 20 and require other analgesics.
Results:

Analgesic effect within 2 h of the treatment with Bing-Chan tincture

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Significantly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Worsened</th>
<th>Total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>40</td>
<td>25</td>
<td>11</td>
<td>4</td>
<td>0</td>
<td>90%</td>
</tr>
<tr>
<td>Control</td>
<td>40</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>5</td>
<td>37.5%</td>
</tr>
</tbody>
</table>

Analgesic effect after 1 week treatment with Bing-Chan tincture

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Significantly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Worsened</th>
<th>Total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>40</td>
<td>12</td>
<td>19</td>
<td>6</td>
<td>3</td>
<td>77.5%</td>
</tr>
<tr>
<td>Control</td>
<td>40</td>
<td>0</td>
<td>8</td>
<td>26</td>
<td>6</td>
<td>20%</td>
</tr>
</tbody>
</table>

Author’s conclusions:

- Bing-Chan tincture is an effective and rapid-acting analgesic preparation.
- Acts within 15 min of application and lasts for 3-4 h.
- The associated side effect is minimal.
- The preparation is not addictive.
Pharmacological basis of Chinese herbs for pain

1. Yan-Hu-Suo 延胡索 and \( \delta \)-tetrahydropalmatine (\( \delta \)-THP) 延胡索乙素

- *Yan-Hu-Suo* 延胡索 is the dried tuber of *Corydalis yanhusuo* W.T. Wang;
- It has the therapeutic functions of invigorating blood circulation and regulating qi movement and stopping pain; and
- Clinically, it is indicated for various pain such as angina, headache, stomachache, hypochondriac pain and dysmenorrhea.

\( \delta \)-tetrahydropalmatine (\( \delta \)-THP) 延胡索乙素

- The main constituent responsible for analgesic action of *Yan-Hu-Suo*.
- Its antinociceptive mechanism involves neither antipyretic nor narcotic pathway.
- Exhibits no affinity for the opiate receptors, but
- Elicits antinociception via antagonistic effect on the D2 dopamine receptors.
• Commonly used in China as a non-antipyretic and non-narcotic analgesic under the trade name of Rotundine 頭痛定 for peptic ulcerative pain, migraine, headache, post-partum pain, dysmenorrhea and pain-caused insomnia.

• Can be delivered through oral (60-120 mg, q.i.d) or intramuscular (60 mg) administration.

2. *Gao-Wu-Tou* 高烏頭 and Lappaconitine hydrobromide (LH) 氫溴酸高烏甲素

• *Gao-Wu-Tou* 高烏頭 is the root of *Aconitum sinomoutanum* Nakai.

• It has the therapeutic functions of wind expelling, dampness relieving, blood stasis removing and pain stopping, and

• Is indicated for various pains such as rheumatic and rheumatoid arthritis and cancer pain.
Lappaconitine hydrobromide (LH) 氫溴酸高烏甲素

- is the hydrobromide salt of lappaconitine, a diterpene alkaloid found in *Aconitum sinomoutanum*.
- Was approved in China in 1982 as a non-opioid prescription drug for Three-step Analgesic Ladder for Cancer Treatment (癌症病人三階梯止痛療法).
- Is a non-dependent analgesic.
- Administration routes: epidural, i.v., oral in tablet, or topical in plaster form.

Lappaconitine hydrobromide (LH) 氫溴酸高烏甲素 (cont’d)

- Possesses potent analgesic effect on cancer pain similar to pethidine with slower but longer-lasting action.
- Has no dependency and withdrawal symptoms and accumulating toxicity.
- Commonly used for mild to moderate cancer pain.
- Or used as adjuvant therapy to reduce the dose of morphine.
LH is also used for:

- Post-operative pain;
- Peptic ulcerative pain;
- Shingle-related neuralgia, especially in elderly patients;
- Arthritic and sciatic pain; and
- Pain of urinary tract syndrome.

Analgesia of Lappaconitine: Mechanisms of action

- General analgesia - Anti-inflammatory effect through inhibition of the production of COX and PGS.
- Central analgesia - achieved through modulating the amount of monoamine transmitters such as 5-HT and noradrenalin in the brain.
- Action sites are similar to those of morphine i.e. periaqueductal gray (PAG) and nucleus raphe magnus (NRM), but via different mediators.
- Is independent of opium receptors.
Is it effective? – systematic review of published literature

**Objective:**
- To evaluate the effectiveness and safety of Chinese herbal medicine for alleviating cancer pain when compared to placebo or conventional treatment.

**Methods:**
- systematic review and meta-analysis.

**Inclusion criteria:**

*Types of studies*
- Randomized controlled trials (RCTs).

*Types of participants*
- Patients with cancer-related pain, which is believed to be directly associated with the development of the cancer.
**Types of intervention**

- The treatment included Chinese herbal medicine, involving extracts from herbs, single or a mixture of herbal preparations regardless of their compositions, formula forms or administration route, and compared with placebo or conventional treatment.
- Those studies on the combination therapy of different approaches of Chinese medicine were excluded.

**Types of outcome measures**

- Pain intensity/pain relief reported by patient;
- Analgesic consumption.
Information sources

English databases
Medline, Embase, and CENTRAL

Chinese databases
CBM and CM-online

Search strategy:

- Search strategy was developed around free-texts or subject headings about pain, cancer and Chinese herbal medicine.
- The search strategies for Medline and CBM were listed as follows:
**Medline**

- 1. exp Pain/ or exp Neuralgia/ or exp Analgesics/
- 2. (pain or neuralgia or analgesic$).mp.
- 3. 1 or 2
- 4. exp Neoplasms/
- 5. (cancer or tumor).mp.
- 6. 4 or 5
- 7. 3 and 6
- 8. exp Medicine, Chinese Traditional/ or exp Drugs, Chinese Herbal/
- 9. chinese herbal medicine.mp. or chinese medicine.mp.
- 10. 8 or 9
- 11. 7 and 10
- 12. limit 11 to humans

**CBM and CM-online**

- **Search strategy in Chinese**
  - 1. (疼痛 or 痛證 or 鎮痛 or 止痛 or 麻醉) and (癌 or 瘤瘤)
  - 2. (癌痛)
  - 3. 1 or 2
  - 2. (中醫 or 中藥 or 植物藥 or 草藥)
  - 3. 隨機 or 安慰 or 盲法 or 雙盲 or 單盲 or 三盲
  - 4. 1 and 2 and 3
  - 5. limit to human
Results – 1. Search results

Flow diagram showing the search process and study selection

Studies identified from databases and other sources (n=753)

Duplicate records excluded (n=69)

Articles screened for titles and abstracts (n=684)

Irrelevant records excluded (n=594)
Articles whose full texts were not available (n=2)

Full-text of RCTs retrieved for detailed evaluation (n=88)

Included studies for review (n=7)

Chinese herbal medicine vs. placebo (n=3)
Included for meta-analysis (n=3)

Chinese herbal medicine vs. analgesics (n=4)
Included for meta-analysis (n=2), 2 studies were excluded for meta-analysis due to the high risk of bias introduced by high dropout rates (>20%)
**Results – 2. Effect results**

(1) **Chinese herbal medicine vs placebo**

- **Outcome 1**: pain reduction (measured by the proportions of effectiveness or otherwise)
  - effective means pain is alleviated,
  - not effective means pain is not alleviated or even aggravated.

There is a significant difference between CHM and placebo in relieving cancer pain favoring CHM treatment.
Outcome 2: Analgesic (morphine) consumption

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chinese herbal medicine</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>53.07</td>
<td>81.02</td>
<td>-27.95</td>
<td>IV, Random, 95% CI [-36.16, -19.74]</td>
</tr>
<tr>
<td>SD</td>
<td>16.51</td>
<td>20.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.67 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chinese herbal medicine showed statistically significant effect on reducing the consumption of morphine when compared to placebo (mean difference 27.95mg, 95%CI 19.74 to 36.16).

(2) Chinese herbal medicine vs analgesics

- Outcome 1: pain reduction (measured by the proportions of effectiveness or otherwise)
  - effective means pain is alleviated,
  - not effective means pain is not alleviated or even aggravated.
The analgesics used in the two studies were paracetamol/codeine phosphate (Wei 2003) and indomethacin (Huang 2004), respectively.

The proportion of patients whose pain was alleviated by CHM was similar to that by paracetamol/codeine phosphate (Wei 2003) or indomethacin (Huang 2004).

Table 1. Treatment characteristics of the included studies on Chinese herbal medicine for cancer pain.
<table>
<thead>
<tr>
<th>Study</th>
<th>Compositions</th>
<th>Administration route</th>
<th>Dosage</th>
<th>Treatment duration (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 1988</td>
<td>蟾酥膏 (蟾酥、生川烏、七葉一枝花、紅花、莪朮、冰片等)，製成橡皮膏</td>
<td>Paste on the pain area</td>
<td>Once per day</td>
<td>7</td>
</tr>
<tr>
<td>Huang 2009</td>
<td>蟾理通膏 (白藥膏、蟾酥、制馬錢子、毛麝香、寮刁竹、大梅片、金牛皮、冰片等)</td>
<td>Paste on the pain area</td>
<td>Twice per day</td>
<td>10</td>
</tr>
<tr>
<td>He 2007</td>
<td>康艾注射液 (黃芪、人參、苦參) and 5% glucose solution 40ml or saline solution 250ml</td>
<td>Intravenous Infusion</td>
<td>Once per day</td>
<td>21</td>
</tr>
<tr>
<td>Wei 2003</td>
<td>天蟾膠囊 (夏天無、制川烏、蟾酥、祖司麻、白芷、白芍、白屈菜、秦艽、川芎、甘草等)</td>
<td>Oral intake</td>
<td>3 capsules per time, 3 times per day</td>
<td>5</td>
</tr>
<tr>
<td>Huang 2004</td>
<td>溫陽止痛膠囊 (熟地黃、鹿茸、肉桂、白芥子、甘草等)</td>
<td>Oral intake</td>
<td>4 capsules per time, 3 times per day</td>
<td>7</td>
</tr>
<tr>
<td>Chen 2000 &amp; Lu 2001</td>
<td>桂參止痛合劑 (由肉桂、細辛、黨參、杜仲等)</td>
<td>Oral intake</td>
<td>50ml per time, once every 8 hours</td>
<td>7</td>
</tr>
</tbody>
</table>

**Conclusions**

- There is some evidence to show that Chinese herbal medicine may reduce the cancer pain intensity and exert similar pain relief effect similar to some analgesics.
- The conclusions drawn are off-set by methodological limitation such as no assessment of placebo blinding effect, high loss to follow-up and the low number of clinical trials.
- More information is also needed about the adverse effects of the treatment of Chinese herbal medicine.
- Further well-designed studies are needed to establish the efficacy and safety of Chinese herbal medicine for cancer pain.
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