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A Systematic Review and Meta-Analysis of Randomized Controlled Trials on Chuna Manual Therapy for Cervicogenic Headache

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Objectives: We conducted this study to evaluate the efficacy of Chuna Manual Therapy (CMT) for treatment of cervicogenic headache (CeH) through systematic review and Meta-analysis of randomized controlled trials (RCTs) as a preceding research to further research the effective of Chuna Manual Therapy for patients who suffered from CeH.

Methods: We conducted a systematic review and meta-analysis by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched the studies from MEDLINE, Elsevier-EMBASE, The Cochrane Library, CAJD, KISS, KMBase, Korean Traditional Knowledge Portal, NDSL, and OASIS. The studies selected only in randomized controlled trials. We selected the chosen studies by the selection and the exclusion criteria, and evaluated the quality of the selected studies using the Jadad score and the Cochran ROB tool. We used the Visual Analogue Scale score (VAS) and Clinical total Effective Rate (CER) for the results and analyzed the results of the included studies using RevMan 5.3 software provided by the Cochran library.

Results: We included 20 RCTs, including 1,673 subjects, in the systematic review and meta-analysis. After the intervention, the CMT group showed better results than the pharmacotherapy group, the physiotherapy group, and the combined treatment group. The CMT group showed a good effect on the CER and the VAS but showed a significant heterogeneity compared to the pharmacotherapy group.

Conclusions: The CMT as monotherapy might have benefits on Cervicogenic Headache patient. Further well-designed studies need to be conducted.

Key Words: Cervicogenic headache, Chuna manual therapy, Systematic review, Meta-analysis.

I. INTRODUCTION

Headache is a common complaint with prevalence in the general population such as children and adults of about 16%. It is divided into primary headache and secondary headache by factors[1-2].

According to the International Headache Society classification (ICHD-3), the secondary headaches are classified as Headache attributed to trauma or injury to the head and/or neck, Headache attributed to cranial or cervical vascular disorder, Headache attributed to non-vascular intracranial disorder, Headache attributed to infection, Headache attributed to disorder of homeostasis, Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure, and Headache attributed to psychiatric disorder. Especially Cervicogenic headache (CeH) is including headache attributed to trauma or injury to the head and/or neck, headache pain attributed to disorder of the cranium, neck or cervical structure[3].

Cervicogenic headache defined as headaches originating from cervical spine structures including cervical facet joints, cervical intervertebral discs, skeletal muscles, connective tissues, and neurovascular structures is a secondary headache characterized by unilateral headache, and symptoms and signs of neck involvement. It is heavily influenced by neck movement, head position or external pressure of the upper cervical or occipital region on the inconvenient region[4,5].

The prevalence of CeH varies in the general population depending on the diagnostic criteria, i.e. 1.0% to 4.6% applying according to criteria in the Cervicogenic Headache International Study Group (CHISG) while it was 2.5 % applying the International Headache Society (IHS) criteria[6].

On the pathological point of view, CeH may originate from dysfunction of various anatomic structures in the cervical region. In particular, the dysfunction of the trigerminal and upper three cervical spinal nerves is likely to lead to the headache. That is, improvement of cervical dysfunction significantly alleviates symptoms[3,7].

CeH is usually caused by trauma of the neck, and is often caused by dystonia due to poor posture, spinal stenosis, and herniation of cervical intervertebral disc[8].

Generally, Treatment of CeH is to using the pharmacological intervention such as a painkiller, or non-pharmacological intervention such as the ganglionic blockade using local anesthetic, occipital nerve blockade and rami medialis blockade of intervertebral joint in western medicine[9,10].

In Korean medicine, Acupuncture, Pharmacoacupuncture, Mini/scalpel Acupuncture (MA), Chuna Manual Therapy (CMT) are using for intervention of CeH and multiple studies on CeH are actively proceeding[11-14].

Especially, CMT is a specialized type of manual therapy where the practitioner uses manual and/or physical force with optional devices to apply appropriate correcting force to specific body areas to treat various dysfunctions and pathophysiologic conditions[15].

CMT has a good effect to improve the structural problems of the human body, and it is estimated to be very effective in treating CeH, but there are barely a few domestic studies[14,16,17].

Thus, This study is conducted to evaluate the efficacy of CMT for treatment of CeH through systematic review and Meta-analysis of randomized controlled trials (RCTs) as a preceding research in order to further research the effective of CMT for patients suffered from CeH.

II. METHODS

1. Data sources and searches

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[18].

The databases were searched from their inception through August 31, 2018. The literature search was performed on August 1, 2018 by two investigators, who are Korean medical doctors. Results published in English, Chinese, Korean were considered. Data were recorded and assessed using Microsoft Excel 2010.

The gray literature was excluded. We also performed a manual search to find the ongoing clinical studies. The reference lists of included studies were screened to confirm that there are missing studies.

1) Identifying studies

International Electrical database (English)

- MEDLINE
- Elsevier-EMBASE
- Cochrane Library Database

Chinese database (Chinese)

- CAJD (China Academic Journal network publishing Database)

Domestic databases (Korean)

- KISS (Korean-studies Information Service System)
- KMBase (Korean Medical database)
- Korean Traditional Knowledge Portal
- NDSL (national discovery for science leaders)
- OASIS (Oriental Medicine Advanced Searching Integrated System)

2) Key words

The search terms:

- In English, Chinese, and Korean: 'Post-traumatic headache*[MeSH term]', 'Cervicogenic headache', 'Cervical headache', 'Headache of cervical origin', 'Craniocervical region in headache', '颈源性头痛', '颈枢部性头痛', '颈枢因性头痛', '颈枢性头痛', '颈部性头痛', 'Chuna', 'Tuina', 'Spinal manipulation', 'Manipulative therapy', 'Chiropractic', 'Massage therapy', 'Osteopathic treatment', 'Spinal mobilization', 'Manual therapy', '推拿' , '手法', '경추인성 두통', '경추성 두통', '경부성 두통', '추나', '수기치료', '카이로프랙틱', '척추교정', '도수치료', '도수치료' and '정골요법'
- Through consultation with CMT specialist, 'Spinal manipulation', 'Manipulative therapy', 'Chiropractic', 'Massage therapy', 'Osteopathic treatment', 'Spinal mobilization', 'Manual therapy' were judged as CMT.

2. Study selection

The study selection was performed independently by two reviewers with disagreement resolved by discussion and adjudication. Duplication of studies was excluded using EXCEL database by comparing the title, the abstract, and author key words published. The CAJ Databases did not allow logical searches with AND, so we used simple combinations of the search words. We selected in the studies of CMT used as an intervention, but the CMT methods were not limited. Only CMT interventioned studies were selected and CMT combined another treatment were excluded. Inappropriate studies were excluded by examining the title and the abstract. All papers with at least an abstract in English were included.

1) Types of studies

Studies mentioning randomized controlled trials (RCTs) of CMT for CeH were considered. And a quasi-random method was allowed. Studies that did not mention RCTs, studies of not using a quasi-random method at least, case series, observational, cohort, case control, qualitative studies, Uncontrolled trials and laboratory studies were excluded.

2) Types of participants

The patients selected were diagnosed with CeH clinically. Studies involving pediatric participants (<19 year) or participants unrelated with headache of cervical origin are excluded. No restrictions to gender and race were imposed.

3) Types of intervention

The intervention should be CMT only. In this study, the intervention was included such as Spinal manipulation, Manipulative therapy, Chiropractic, Massage therapy, Osteopathic treatment, Spinal mobilization, Manual therapy through experts advice whether it is applicable to the act of CMT. Other forms of treatments (unrelated CMT such as Qi gong etc.) were excluded. Studies that assessed the combined treatment effect of CMT with Electroacupuncture, Laser therapy, Pharmacoacupuncture, Mini scalpel acupuncture, Auricular acupuncture, Pharmacotherapy, Physiotherapy were excluded.

4) Types of control

We excluded studies that included controls that corresponded to CMT behavior such as Massage therapy (control), CMT (control) itself, Complex therapy (control) including CMT. Usual care or Sharm CMT were included allowedly.

5) Types of outcome measures

The outcome measure was set to Severity of CeH pain and Clinical total Effective Rate (CER) at the End of treatment (EOT) as the primary outcome. CeH Pain severity was measured by Visual Analogue Scale score (VAS) and the CER calculated by the change in CeH symptom. The CER was calculated using the following formula: CER=N1+N2/N, where N1, N2, and N are the number of patients who are markedly improved, improved, and who comprise the sample size, respectively. Headache numerical rating scale (NRS), Headache Frequency, Headache Duration, Headache Intensity, Transcranial Doppler (TCD), Range of Motion (ROM), Mcgill Pain Index, Cervical vertebra activity score were the secondary outcome.

3. Data extraction

Data extraction was performed independently by two unblinded investigators and discrepancies were resolved through discussion. Data from the articles were validated and extracted using a predefined data extraction form. Study characteristics were study design, sample size, age range, treatment duration, intervention, control, adverse events and outcome.

4. Risk of bias assessment

To assess the methodological quality of RCTs included, the Risk of Bias tool provided by the Cochrane Collaboration was used, and we obeyed the principles for assessing risk of bias[19]. Because baseline imbalance in factors that are strongly related to outcome measures can cause other potential biases in the estimation of an intervention effect in RCTs.

5. Data synthesis

The quantitative data of primary and secondary outcomes were combined and meta-analysis was performed according to effects of CMT, using RevMan software version 5.3 (Cochrane, London, UK).

6. Identifying heterogeneity

A random-effect model was considered possible clinical heterogeneity among the included studies using the chi-square test, the tau^2 test, and Higgins I^2 statistics[18].

III. RESULTS

1. Study selection

The titles and/or abstracts of 509 studies were screened, and the full texts of 202 articles were reviewed (Fig. 1). Ineligible studies reviewed in titles and/or abstracts were excluded (n=188). Of the 202 articles reviewed in full text, 20 studies were identified

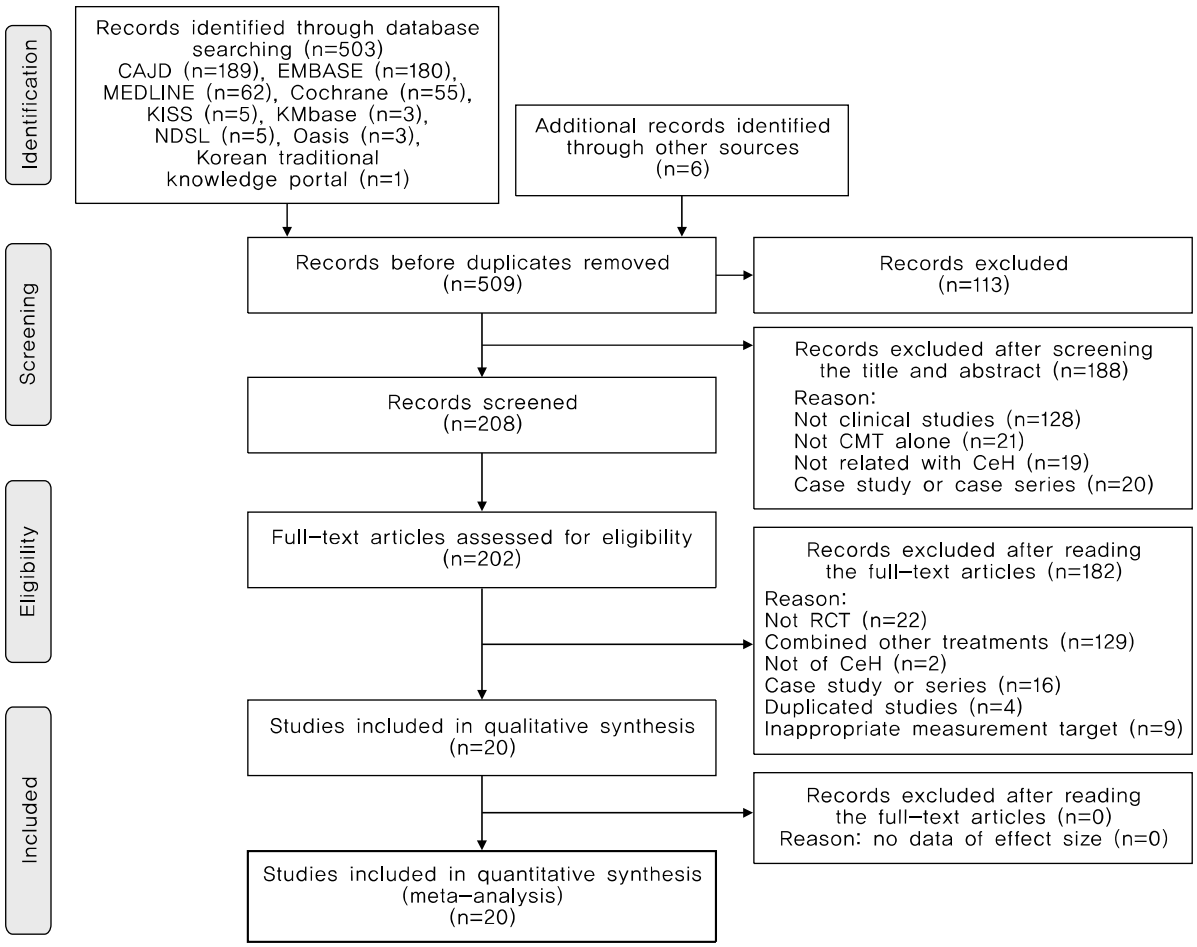

Fig. 1. PRISMA flowchart of study selection.

for inclusion in systematic review (Luan et al. 2002), (Sun 2005), (Jiang 2005), (Chen et al. 2007), (Wang et al. 2007), (Yan 2007), (Tang et al. 2008), (Huang 2008), (Wang et al. 2008), (Wei et al. 2008), (Wei 2009), (Wang et al. 2009), (Lee et al. 2011), (Yu 2011), (Quan et al. 2011), (Liu et al. 2014), (Xu et al. 2016), (Ding 2017), (Aleksander et al. 2017), (Wang et al. 2018)[20-39]. Ineligible studies reviewed in full text were excluded (n=121), reason that they were RCTs but not of CeH (n=2), not RCTs (n=22), combined other treatment (n=129), case study or series (n=16), duplication studies (n=4), inappropriate measurement targets (n=9).

20 studies were identified for inclusion in meta-analysis (Luan et al. 2002), (Sun 2005), (Jiang 2005), (Wang et al. 2007), (Yan 2007), (Chen et al. 2007), (Huang 2008), (Wei et al. 2008), (Wei 2009), (Wang et al. 2009), (Lee et al. 2011), (Quan et al. 2011), (Yu 2011), (Liu et al. 2014), (Xu et al. 2016), (Ding 2017), (Tang et al. 2008), (Aleksander et al. 2017), (Wang et al. 2018).

2. Study description

1) Characteristics of included studies

In all, 20 studies were included for systematic review and all studies for meta-analysis. The summary of the included RCTs are presented in Table 1 and 2.

19 trials originated from the China ((Luan et al.

Table 1. General Characteristics of Included RCTs of CMT for CeH

First author (year)/country	Design	Condition	Number (registered)	Number (analysed)	Sample (mean age or range) /duration (mean or range)
Luan (2002)/China	RCT	Cervicogenic headache	n.r/n.r	52/50	(A) 42±n.r / n.r (B) 41±n.r / n.r
Sun (2005)/China	RCT	Cervicogenic headache	n.r/n.r	28/28	(A) 38.4±4.2 yr / 1.60±0.33 yr (B) 37.1±5.5 yr / 1.50±0.42 yr
Jiang (2005)/China	RCT (3-arm)	Headache of cervical origin	19/18/21	19/18/21	(A) 38.2 yr±n.r / 15.3M±n.r (B) 40.3 yr±n.r / 13.9M±n.r (C) 38.9 yr±n.r / 16.1M±n.r
Wang (2007)/China	RCT	Cervicogenic headache	n.r/n.r	30/30	(A) 45.8 yr±n.r / 1 d～20M (B) 44.2 yr±n.r / 3～24M
Yan (2007)/China	RCT	Cervicogenic headache	n.r/n.r	49/48	(A) 17～65 yr / 1 d～16 yr (B) 19～62 yr / 2 d～20 yr
Chen (2007)/China	RCT	Cervicogenic headache	n.r/n.r	36/34	(A) 41.32±11.27 yr / 24.34±6.52M (B) 43.68±16.63 yr / 18.51±8.43M
Huang (2008)/China	RCT	Cervicogenic headache	n.r/n.r	40/40	(A) 37.6 yr±n.r / 4M±n.r (B) 36.5 yr±n.r / 5M±n.r
Wang (2008)/China	RCT	Cervicogenic headache	n.r/n.r	60/60	(A) 42.5±7.8 yr / 2.6±1.9 yr (B) 43.3±8.1 yr / 2.6±1.8 yr
Tang (2008)/China	RCT	Cervicogenic headache	n.r/n.r	32/32	(A) 40.24±7.28 yr / n.r (B) 41.14±6.78 yr / n.r
Wei (2008)/China	RCT	Cervicogenic headache	n.r/n.r	37/23 (50/30)	(A) 46 yr±n.r / 90M±n.r (B) 48 yr±n.r / 99M±n.r
Wei (2009)/China	RCT	Cervicogenic headache	n.r/n.r	40/38	(A) 48 yr±n.r / 1d～15 yr (B) 47 yr±n.r / 1d～16 yr
Wang (2009)/China	RCT	Cervicogenic headache	n.r/n.r	50/44	(A) 35.5 yr±n.r / 3M～15 yr (B) 34.3 yr±n.r / 2M～13 yr
Lee (2011)/China	RCT	Cervicogenic headache	60/30	60/30	(A) n.r/n.r (B) n.r/n.r
Quan (2011)/China	RCT	Cervicogenic headache	n.r/n.r	60/60	(A) 37.43±5.45 yr / 70.32±6.59 d (B) 38.51±4.78 yr / 69.45±7.01 d
Yu (2011)/China	RCT	Cervicogenic headache	n.r/n.r	50/50	(A) n.r / n.r (B) n.r / n.r
Liu (2014)/China	RCT	Cervicogenic headache	n.r/n.r	56/56	(A) 51.30±2.87 yr / 5.89±4.21M (B) 52.17±3.56 yr / 6.11±2.34M
Xu (2016)/China	RCT	Cervicogenic headache	n.r/n.r	30/30	(A) 42～61 yr/2～15M (B) 41～62 yr/2～16M
Ding (2017)/China	RCT	Cervicogenic headache	n.r/n.r	100/100	(A) 36.7 yr±n.r / 2M～13 yr (B) 35.5 yr±n.r / 3M～15 yr
Aleksander (2017)/Norway	RCT (3-arm)	Cervicogenic headache	n.r/n.r/n.r	4/4/4	(A) 36.0±12.8 yr / 7.3±3.3 yr (B) 49.8±12.3 yr / 8.5±1.3 yr (C) 48.0±9.8 yr / 13.8±10.4 yr
Wang (2018)/China	RCT	Cervix headache	n.r/n.r	36/34	(A) 32.10±4.26 yr / 26.33±11.38M (B) 33.73±5.03 yr / 25.48±11.38M

RCT: Randomized Clinical Trial, CMT: Chuna Manual Therapy, CeH: Cervicogenic headache, n.r: not reported, yr: year, M: month.

2002), (Sun 2005), (Jiang 2005), (Chen et al. 2007), (Wang et al. 2007), (Yan 2007), (Tang et al. 2008), (Huang 2008), (Wang et al. 2008), (Wei et al. 2008), (Wei 2009), (Wang et al. 2009), (Lee et al. 2011), (Yu 2011), (Quan et al. 2011), (Liu et al. 2014), (Xu et al. 2016), (Ding 2017), (Wang et al. 2018)), one trials from Norway (Aleksander et al. 2017).

In 20 RCTs comparisoning 1,673 participants were included for the systematic review. They were all diagnosed CeH and participated in studies. Mean ages of

Table 2. Intervention Characteristics and Main Outcomes of Included RCTs of CMT for CeH

First author (year) /country	Intervention group	Control group	Outcome measure	Result	AE
Luan (2002)/China	(A) CMT 1 time/day n.r min/time for 10 days	(B) Pharmacotherapy sibelium 10 mg 1 time/day for 10 days	1. CER	1. (A)>(B), ($p<0.05$)	n.r
Sun(2005)/China	(A) CMT 1 time/day 18~22 min/time for 15 times	(B) Pharmacotherapy Chlorzoxazone Tablets 0.5 g 3 times/day ibuprofen, 2 time/day jingfukang granules, 2 times/day	1. CER	1. (A)>(B), ($p<0.01$)	n.r
Jiang (2005)/China	(A) CMT 1 time/4~5 day n.r min/time for 2~3 times	(B) Physiotherapy Laser irradiation 1 time/day for 5 days (C) Complex therapy Laser irradiation therapy and CMT	1. VAS	1. (A)>(B), ($p<0.05$)	none
Wang (2007)/China	(A) CMT 3 times/week 20 min/time for 10 times	(B) Pharmacotherapy Yangxue Qingnao Granules 4 g, 3 times/day for 10 days	1. VAS 2. CER	1. (A)>(B), ($p<0.05$) 2. (A)>(B), ($p<0.05$)	n.r
Yan (2007)/China	(A) CMT 1 time/2 days n.r min/time for 6 times	(B) Pharmacotherapy Ibuprofen 0.2 g, 2pills 3 times/day for 6 days	1. CER	1. (A)>(B), ($p<0.01$)	n.r
Chen (2007)/China	(A) CMT 1 time/2 days 20~30 min/time for 20 days	(B) Physiotherapy TENS, 100 Hz, 250 μs 1 time/2 days 20 min/time for 10 times	1. CER 2. ROM 3. Headache NRS 4. Headache frequency 5. Headache duration	1. (A)>(B), ($p<0.05$) 2. NSD 3. (A)>(B), ($p<0.01$) 4. (A)>(B), ($p<0.01$) 5. (A)>(B), ($p<0.01$)	n.r
Wang (2009)/China	(A) CMT 1 time/day 30 min/time for 10 days	(B) Physiotherapy Traction therapy 1 time/day for 10 days	1. VAS 2. CER 3. TCD	1. (A)>(B), ($p<0.01$) 2. (A)>(B), ($p<0.05$) 3. (A)>(B), ($p<0.05$)	none
Lee (2011)/China	(A) CMT 1 time/day n.r min/time for 10 times	(B) Physiotherapy Ultra laser treatment 1 time/1~2 days 15 min/time for 10 times	1. VAS 2. McGill Pain Index	1. NSD 2. NSD	n.r
Quan (2011)/China	(A) CMT 2 time/week 3 min/time for 2 weeks	(B) Pharmacotherapy Meloxicam Tablets 7.5 mg, 1 time/day for 2 weeks	1. VAS 2. CER	1. (A)>(B), ($p<0.01$) 2. (A)>(B), ($p<0.01$)	n.r
Yu (2011)/China	(A) CMT 1 time/day n.r min/time for 10 days	(B) Pharmacotherapy Difenidol 2pills Oryzanol 2pills vitamin B1 2pills 3 times/day for 10 days	1. CER	1. (A)>(B), ($p<0.05$)	n.r
Liu (2014)/China	(A) CMT 1 time/3~4 days n.r min/time for 21 days	(B) Pharmacotherapy ibuprofen 0.2 g, 3 times/day for 6 days esomeprazole 20 mg, 1 time/day for 6 days	1. VAS 2. CER	1. (A)>(B), ($p<0.05$) 2. (A)>(B), ($p<0.05$)	n.r
Xu (2016)/China	(A) CMT 1 time/day 20 min/time for 10 days	(B) Pharmacotherapy Meloxicam 7.5 mg 1 time/day for 10 days Flunarizine hydrochloride 5 mg 1 time/day for 10 days	1. CER	1. (A)>(B), ($p<0.05$)	n.r
Ding (2017)/China	(A) CMT 1 time/day 30 min/time for 10 days	(B) Physiotherapy Traction therapy 1 time/day for 10 days	1. VAS 2. CER	1. (A)>(B), ($p<0.05$) 2. (A)>(B), ($p<0.05$)	n.r
Aleksander (2017) /Norway	(A) CMT 1 time/day n.r min/time for 12 times	(B) Sham manipulation 12 intervention sessions for 3M (C) Usual management (Medication without receiving manual intervention) 12 intervention sessions for 3M	1. Headache frequency 2. Headache duration 3. Headache intensity 4. Headache index	n.r	none

Table 2. Continued

First author (year) /country	Intervention group	Control group	Outcome measure	Result	AE
Wei (2009)/China	(A) CMT 1 time/day 20～25 min/day for 10 days	(B) Physiotherapy Computerized intermediate frequency therapy 1 time/day 20～25 min/time for 10 days	1. CER	1. (A)＞(B), ($p<0.05$)	n.r
Huang (2008)/ China	(A) CMT 1 time/2 days 5～7 min/time for 20 days (severe symptom: 1 time/day)	(B) Medication therapy Sibiling capsule 10 mg (Flunarizine Hydrochloride) 1 time/day for 20 days Indomethacin 25 mg 3 times/day for 20 days Vitamin B6 20 mg 3 times/day for 20 days	1. CER	1. (A)＞(B), ($p<0.05$)	n.r
Wang (2008)/China	(A) CMT 1 time/day 20 min/time for 15 times	(B) Injection therapy Ligustrazine hydrochloride 0.12 g IV and Adenosine Cobamamide IM for 15 times	1. CER	1. (A)＞(B), ($p<0.05$)	n.r
Wang (2018)/China	(A) CMT 1 time/2 days 20 min/time for 7 times	(B) Acupuncture therapy 1 time/2 days for 7 days 0.30 mm×25 mm needling remaining time: 20 min	1. VAS 2. CER 3. Headache score 4. Cervical vertebra activity score	1. (A)＞(B), ($p<0.01$) 2. (A)＞(B), ($p<0.05$) 3. NSD 4. (A)＞(B), ($p<0.05$)	n.r
Tang (2008)/China	(A) CMT 1 time/day 3 min/time for 7 times	(B) Physiotherapy and Pharmacotherapy Traction therapy n.r min/day for n.r Ibuprofen 0.3 g, 2 time/day for 7 days	1. VAS 2. CER 3. Headache frequency	1. (A)＞(B), ($p<0.05$) 2. (A)＞(B), ($p<0.05$) 3. (A)＞(B), ($p<0.05$)	n.r
Wei (2008)/China	(A) CMT 1 time/day n.r min/time for 10 days	(B) Pharmacotherapy Difenidol 2pills Oryzanol 2pills vitaminB1 2pills 3 times/day7 for 10 days	1. CER	1. (A)＞(B), ($p<0.01$)	n.r

AE: Adverse event, CMT: Chuna Manual Therapy, CeH: Cervicogenic headache, n.r: no reported, VAS: Visual Anlog Scale, CER: Clinical total Effective Rate, IV: intravenous, IM: Intra-Muscular, TCD: Trans-cranial Doppler, ROM: Range of motion, NSD: Not significantly difference, NRS: Numeric Rating Scal, M: month, min: minute, TENS: Trans-cutaneuous electrical stimulation.

16 trials were from 32.10 to 52.17 years. 4 trials were uncertain. Mean duration was 1 day to 16 years in range or 69.45 days to 13.8±10.5 years in mean but it is difficult to define the characteristics of participants because many studies had not been described accurately.

All the trials used CMT. In all RCTs, 18 trials were two-armed parallel group design, and two trials were three-armed group design. 6 trials were designed study as CMT versus Physiotherapy (PT) ((Jiang 2005), (Chen et al. 2007), (Wei 2009), (Wang et al. 2009), (Lee et al. 2011), (Ding 2017)). 10 trials were designed as CMT versus Pharmacotherapy ((Luan et al. 2002), (Sun 2005), (Yan 2007), (Wang et al. 2007), (Wei et al. 2008), (Huang 2008), (Yu 2011), (Quan et al. 2011), (Liu et al. 2014), (Xu et al. 2016)). 1 trials were designed as CMT versus Injection therapy (Wang et al. 2008), 1 trials were designed as CMT versus PT and Pharmacotherapy (Tang et al. 2008), 1 trials were designed as CMT versus sharm CMT or usual management (pharmacotherapy) (Aleksander et al. 2017), and 1 trials were designed as CMT versus acupuncture treatment (Wang et al. 2018).

CMT treatment time of 13 trials was from 3 to 30 minutes but 7 trials were not mentioned. In treatment duration, the range of consecutive treatment days was 10 to 21 in 11 trials. 9 trials were not mentioned. And total number of treatment frequency was from 2 to 15 times, most of trials were treated about 10 times.

In designed studies as CMT versus Physiotherapy,

they used traction therapies, laser irradiation therapies, Computerized Intermediate frequency therapy, Transcutaneous electrical Nerve Stimulation (TENS) and in designed as CMT versus Pharmacotherapy, they used various kinds of medications such as Difenidol, Oryzanol, Vitamin B1, Meloxicam, Flunarizine Hydrochloride, Indomethacin, Vitamin B6, Sibelium, Yangxue Qingnao Granules, Ibuprofen.

2) Outcome measures

16 trials examined in this study used VAS or CER as a main outcome measurement (Table 2).

4 trials compared groups between CMT versus PT (Conventional physical therapy such as traction therapies, laser irradiation therapies, Computerized Intermediate frequency therapy and TENS) in VAS ((Jiang 2005), (Wang et al. 2009), (Lee et al. 2011), (Ding 2017)), and there was no significant difference in reducing pain of CEH between CMT and PT in Lee (2011). However in Jiang (2005), Wang et al (2009), Ding (2017) CMT groups were improved significantly compared to PT groups ($p<0.01$ or $p<0.05$). In Jiang (2005), VAS had a significantly change compared to Laser therapy groups ($p<0.05$). In Wang et al (2009) and Ding (2017), there were significantly change in VAS compared to Traction groups ($p<0.01$ and $p<0.05$).

4 trials compared groups between CMT versus PT in CER ((Chen et al. 2007), (Wei 2009), (Wang et al. 2009), (Ding 2017)). In Chen et al. (2007), CER improved significantly compared to TENS groups ($p<0.05$). In Wei (2009), CER improved significantly compared to Intermediate frequency therapy apparatus groups ($p<0.05$). In Wang et al. (2009) and Ding (2017), Both of their CER improved significantly compared to Traction therapy groups ($p<0.05$).

3 trials compared groups between CMT versus Pharmacotherapy in VAS ((Wang et al. 2007), (Quan et al. 2011), (Liu et al. 2014)). They all were significantly reduced VAS compared to Pharmacotherapy groups including herbal medicine and Western medications. In Wang et al. (2007), VAS reduced significantly compared to control group using Yangxue Qingnao Granules (herbal medicine) ($p<0.05$). and in Quan et al. (2011) and Liu et al. (2014), reduced significantly compared to Pharmacotherapy group, too ($p<0.01$ and $p<0.05$).

10 trials compared groups between CMT versus Pharmacotherapy in CER ((Luan et al. 2002), (Sun 2005), (Yan 2007), (Wang et al. 2007), (Wei et al. 2008), (Huang 2008), (Yu 2011), (Quan et al. 2011), (Liu et al. 2014), (Xu et al. 2016)). They all improved CER significantly compared to Pharmacotherapy group ($p<0.01$ and $p<0.05$).

However in some studies, there were no significant result. In Lee (2011), CMT group was compared to Ultra laser therapy group, but there were no significant difference in VAS and Mcgill Pain Index (NSD). In Aleksander et al. (2017), they compared groups among CMT versus sharm CMT or Usual treatment such as Pharmacotherapy (3-arm study). But they did not mentioned results. In Chen et al. (2007), CMT improved in CER ($p<0.05$), Headache NRS ($p<0.01$), Headache frequency ($p<0.01$) and Headache duration ($p<0.01$) but ROM did not significantly (NSD).

3. Risk of bias assessment

For the methodological quality, risk of bias (ROB) using modified Jadad score and the Cochrane Collaboration's tool for assessing ROB were used[18,19]. l8 studies of 20 trials did not mentioned Random sequence generation and all 20 trials did not randomly allocated participants. Furthermore 19 studies excluding one study had high risks of participants and personnel on Reflecting the characteristics of the intervention (CMT). And all trials did not mentioned concerning the blinding of the outcome assessment. Wei et al. (2008), Liu et al. (2014) and Aleksander et al. (2017) showed attrition bias because of drop-outs due to dissat-

isfaction with treatment. Except for only one study, 19 studies showed reporting bias. Especially Wei (2008) was reported differently analyzed number in contents. In other bias, Liu et al. (2014) and Jiang (2005) had a significant difference in duration between the two groups at baseline (Fig. 2).

According to the Jadad scoring system, all 20 trials were randomized in various ways including a quasi-random method. 2 trials used a random number Table of blocked randomization. So 2 trials randomized as appropriate methods ((Wang 2007), (Wei 2009)), No one randomized as inappropriate method and 18 trials did not reported randomization method ((Luan et al. 2002), (Sun 2005), (Jiang 2005), (Yan 2007), (Chen et al. 2007), (Huang 2008), (Wang et al. 2008), (Tang et al. 2008), (Wei et al. 2008), (Wang et al. 2009), (Lee et al. 2011), (Quan et al. 2011), (Yu 2011), (Liu et al. 2014), (Xu et al. 2016), (Ding 2017), (Aleksander et al. 2017), (Wang et al. 2018)).

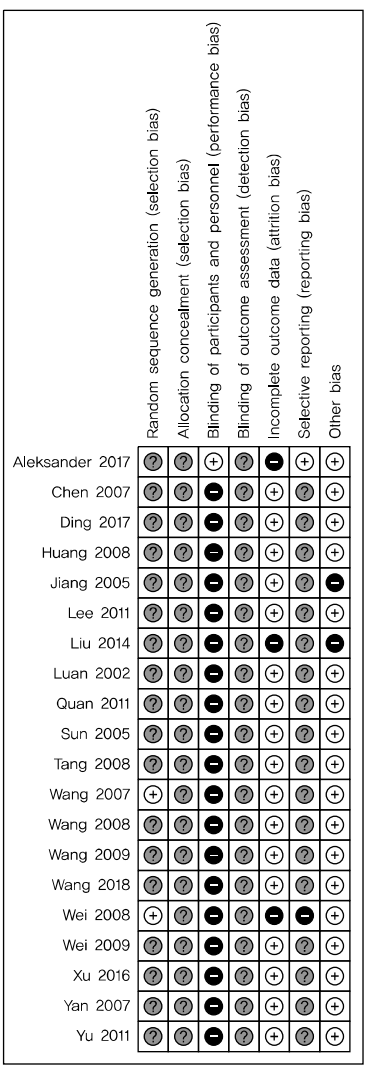

Fig. 2. Risk of bias summary.

Only one trials were double-blinded (Aleksander et al. 2017), and other 19 trials did not mentioned. Thus, one trials obtained a score of 3 (Aleksander et al. 2017), 3 trials received a score of 2 ((Jiang 2005), (Wang 2007), (Wei 2009)), 16 trials received a total score of 1 ((Luan et al. 2002), (Sun 2005), (Yan 2007), (Chen et al. 2007), (Huang 2008), (Wang et al. 2008), (Tang et al. 2008), (Wei et al. 2008), (Wang et al. 2009), (Lee et al. 2011), (Quan et al. 2011), (Yu 2011), (Liu et al. 2014), (Xu et al. 2016), (Ding 2017), (Wang et al. 2018)). Therefore, 19 studies except Aleksander et al. (2017) received scores of negative 1 or 2.

4. Outcome Results

1) VAS change of CMT versus Pharmacotherapy

The data of 3 studies compared Chuna Manual Therapy (CMT) and Pharmacotherapy were synthesis in VAS change (Fig. 3). VAS is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. In this study, VAS was calculated based on feeling of patient as the CeH symptom change after receiving CMT for 4 to 10 times or pharmacotherapies.

2) CER change of CMT versus Pharmacotherapy

The data of 10 studies compared Chuna Manual Therapy (CMT) and Pharmacotherapy were synthesis in CER change (Fig. 4). CER was calculated based on changes in improvement CeH symptom after receiving CMT for 4 to 15 times or pharmacotherapies.

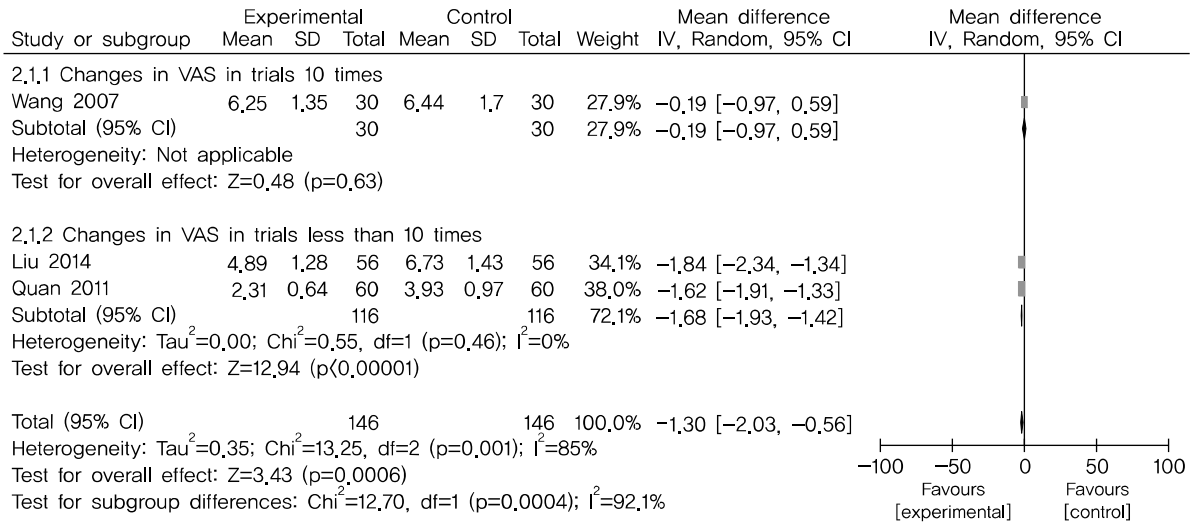

Fig. 3. The forest plot of VAS: Chuna Manual Therapy versus Pharmacotherapy.

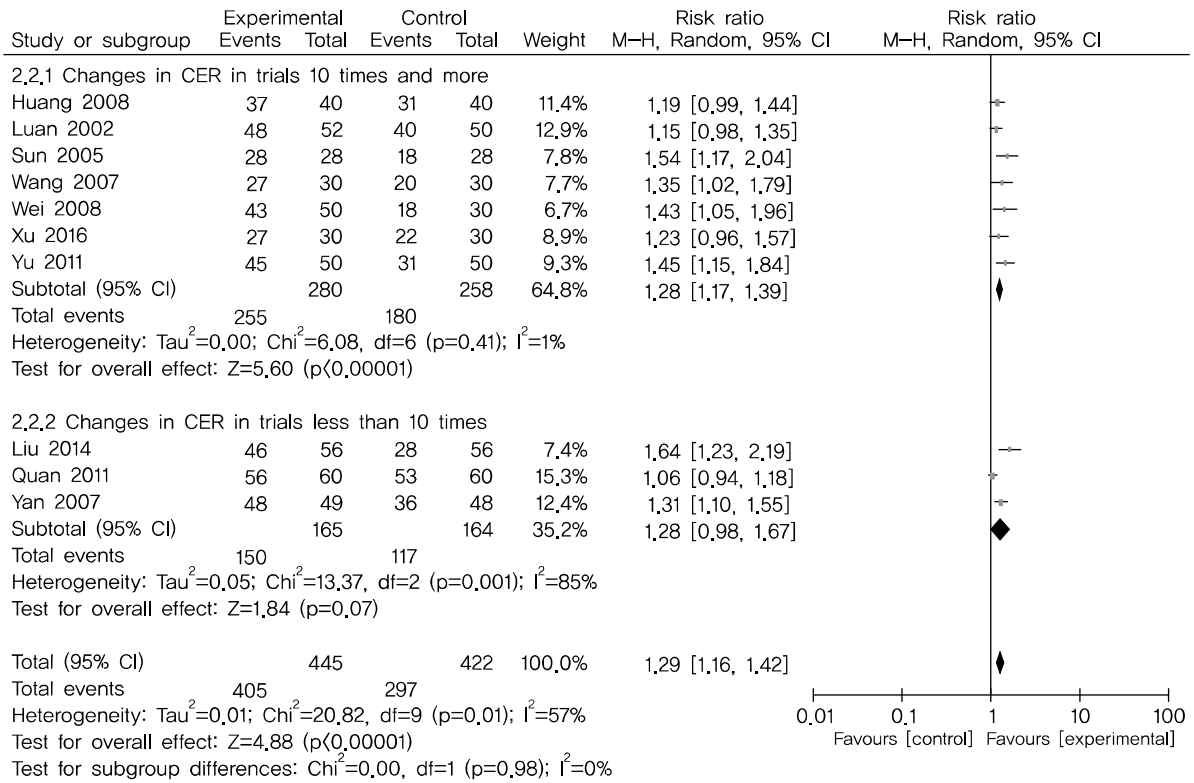

Fig. 4. The forest plot of CER: Chuna Manual Therapy versus Pharmacotherapy.

3) VAS change of CMT versus Physiotherapy

The data of 4 studies compared Chuna Manual Therapy (CMT) and Physiotherapy were synthesis in VAS change (Fig. 5). VAS was calculated based on feeling of patient as the CeH symptom change after re-

ceiving CMT for 2,3 to 10 times or Physiotherapies.

4) CER change of CMT versus Physiotherapy

The data of 4 studies compared Chuna Manual Therapy (CMT) and Physiotherapy were synthesis in CER change (Fig. 6). CER was calculated based on changes in improvement CeH symptom change after receiving CMT for 2,3 to 10 times or Physiotherapies.

5) VAS change of CMT versus Combined therapy

2 studies compared Chuna Manual Therapy (CMT) and Combined therapy group corresponds to usual

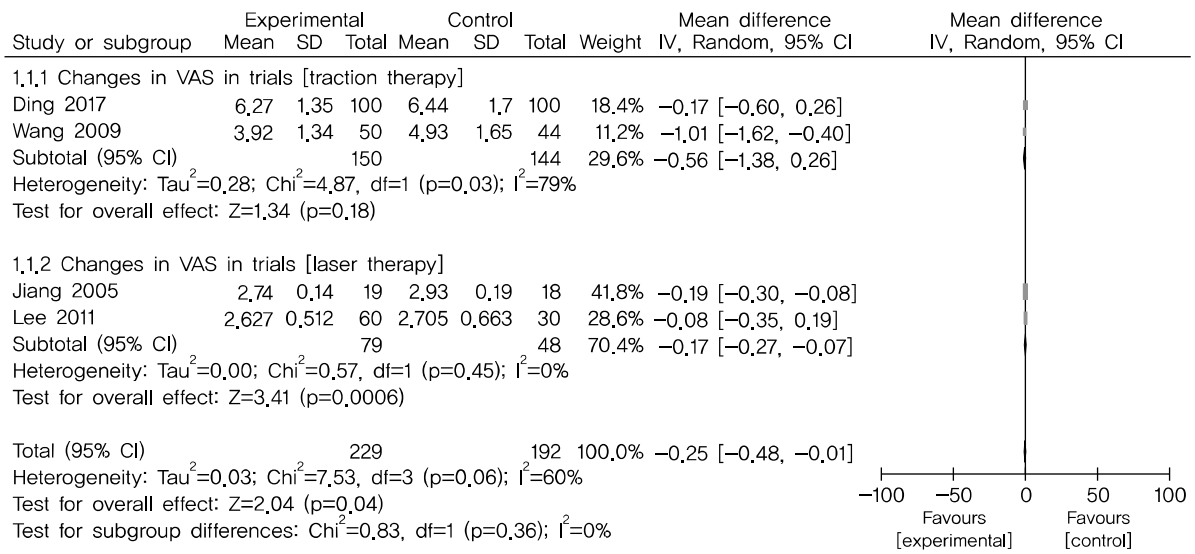

Fig. 5. The forest plot of VAS: Chuna Manual Therapy versus Physiotherapy.

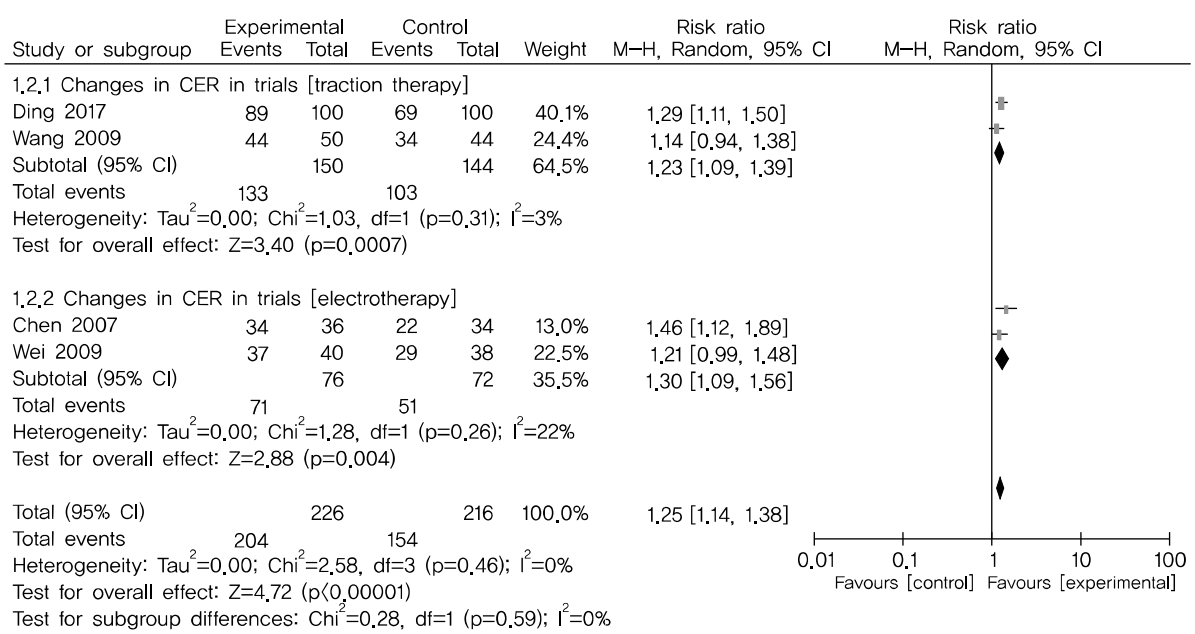

Fig. 6. The forest plot of CER: Chuna Manual Therapy versus Physiotherapy.

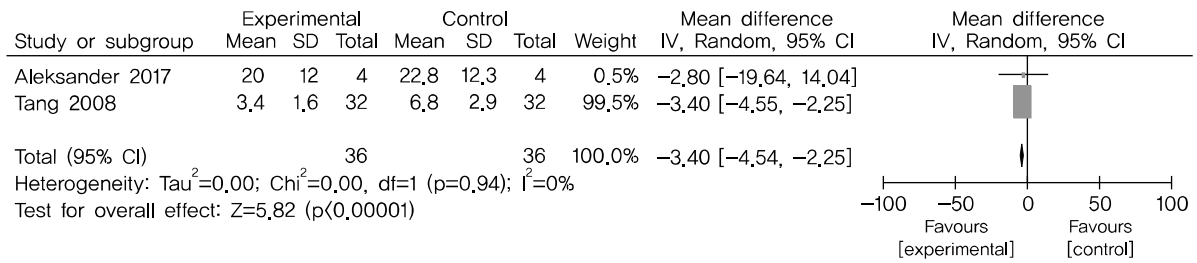

Fig. 7. The forest plot of VAS: Chuna Manual Therapy versus Combined therapies

care. They were synthesis in VAS change (Fig. 7). This VAS was calculated based on feeling of patient as the CeH symptom change after receiving CMT for 7 to 12 times or combined therapies such as Pharmacotherapies, Physiotherapies or both.

6) Safety

In 20 studies analyzed, Jiang (2005), Wang et al. (2009), Aleksander et al. (2017) reported no adverse events. The others did not mentioned. It is unlikely to conclude about the Adverse events of only three of the 20 studies.

IV. DISCUSSION

Chuna Manual Therapy (CMT) is a non-surgical treatment modality that includes the use of skilled hands directed to the patient's spine and extremities for the purpose of treating and restoring a variety of symptoms and conditions. CMT has long been used to treat various diseases, the pain control mechanism underlying the effect of CMT is various. So CMT constitutes a wide variety of different techniques which may be categorized as follows: thrust manipulation, mobilization, static stretching, and muscle energy techniques[40].

Cervicogenic headache (CeH) is a syndrome characterized by chronic hemicranial pain that is referred to the head from either bony structures or soft tissues of the neck. CeH is known to be a problem of the upper cervical vertebrae that the trigeminocervical nucleus is a region of the upper cervical spinal cord where sensory nerve fibers in the descending tract of the trigeminal nerve (trigeminal nucleus caudalis) are believed to interact with sensory fibers from the upper cervical roots[41]. CeH is a typical treatment target of CMT, and it is also a disease that can be encountered frequently in the clinical field.

CMT has been reported to be effective for musculoskeletal disorder including CeH[17,42,43]. CeH occurs from the problem of the cervical region, CMT, a useful tool for spinal therapy, is also a therapeutic tool for CeH. So 3 reviews concluded that there was a effectiveness from previous RCTs of CMT compared to other intervention for improving CeH. but there were no sufficient conclusive evidence of its efficacy[17,42,43]. But, previous studies have shown that heterogeneity is valid, control group of the study was not clear. Presenting reviews of synthesis has some error in application to clinical treatment, as some reviews included trials with tension type headache, migrane, or synthesized several mixed types of treatments with CMT, so these might be not appropriate in assessment of effect of CMT to CeH in general. Thus, in this study, selective intervention was determined as CMT as monotherapy for CeH patients. CMT was the selective intervention, and other treatment modalities such as herb remedies and other types of intervention were all excluded.

All trials described the trials as randomized controlled trials (RCTs) in various ways, the study, which

was not clearly described, was not given a score. All studies had not mentioned concerned with allocation concealment, so they were suspicious of the quality of the study. In blinding of participants and personnel, only one trial mentioned. 19 trials had high risk of blinding of participants and personnel. Also all studies mentioned nothing of blinding of the outcome assessors. 17 studies included no-dropouts but 3 studies had a high risk of incomplete outcome because analyzed number was not same at the beginning of the report and result or the measurement value of reporting is unclear. In other bias, Jiang (2005) and Liu (2014) had a significant difference in duration between the two groups at baseline.

This review aimed to evaluate the clinical effect of Chuna Manual Therapy (CMT) for Cervicogenic Headache (CeH) as monotherapy compared to other intervention. The comprehensive search in this study involved 20 RCTs of CMT for CeH. Based on the results of our study, CMT as a monotherapy significantly reduced Pain or discomfortance of CeH by measured by Clinical total Effective Rate (CER) and Visual Analogue Scale (VAS) after the intervention, with no consistent results regarding CeH totally.

However, there were favorable results for CMT group compared with pharmacotherapy group, physiotherapy group and combined treatment group after the intervention.

CMT group showed improvement effect using CER and VAS compared with pharmacotherapy, but their heterogeneity were significant. Each of the 20 selected studies showed that CMT was effective. Despite the positive results of each study, the heterogeneity of the study group was significant. To further evaluate, subgroup analysis was conducted. Considering the different frequency of treatments between CMT group in VAS, We divided CMT group into subgroup (Treated 10 times and more) and subgroup (Treated less than 10 times). CMT that performed less than 10 times as monotherapy showed significantly difference in VAS compared with pharmacotherapy and showed no heterogeneity. Also CMT that performed more than 10 times as monotherapy was very effective in CER compared with pharmacotherapy. Also CMT group in CER conducted subgroup analysis. In the same way, We divided into two subgroups (Treated 10 times and more) and subgroup (Treated less than 10 times). CMT group that performed 10 times and more showed significantly difference in CER compared with pharmacotherapy and showed no heterogeneity.

Comparing with physiotherapy, CMT group obtained poor result in VAS but in CER showed significant effectiveness. Especially CMT was effective in VAS and CER compared to Traction therapy, Electrotherapy such as TENS and Computerized intermediate frequency therapy, Laser therapy. And compared to combined therapy, CMT was very effective, too.

However, these seemingly positive results about efficacy of CMT for CeH should be interpreted cautiously because of a limited number of studies included in this review, heterogeneities among them and low methodological quality of them[42,44]. NSAIDs are currently regarded as first-line treatment based on extensive evidence, and physiotherapy is also the most commonly used pain treatment method in both East and West. This treatments not only easy but also simple treat to the positive results of economical outcomes, but CMT should not be regarded as a substitute for conventional pharmacotherapy in routine treatment course. However, it may be considered to utilize in the managements of patients having polypharmacy trouble or patients who current treatment is ineffective.

This review has some serious limitations and that should be taken seriously into account. First, the age range of the participants in the included studies varied from 17 to 69 years except unmentioned report, and the range of the disease period of CeH are vary from 1 day to 20 years. Due to these demographic limits,

the analyzed data may not be generalized. Second, some synthesized outcomes of CMT have substantial statistical and clinical heterogeneities included in the quantitative analyses. It may be caused by difference in characteristics of participants. And it will be weaken the reliability of the data. Third, included studies of this paper were evaluated as Low methodological quality. The major responsibility of some studies was the lack of proper method of blinding. However, considering the characteristics of CMT, it was hard to carry out blinding method such as sham CMT. Therefore, there is a need to minimize the elements that can cause other bias, such as blinding of outcome assessor. No trial reported a formal sample size calculation, and inadequate sample size can overestimate the efficacy of CMT. Fourth, 19 of 20 studies in analysis included are published in China, and this may limit the universality of the results of this review. Fifth, since there have been no studies reporting IRB approval, there is a limit to the ethical aspects of the studies involved.

Further studies of higher quality, appropriate sample size via calculation, and long-term are needed to solidify the results of this review. Inclusion criteria about participant and intervention should be clearly specified to determine who could benefit from CMT and which methods of CMT are most effective. The reporting of RCTs should follow Consolidated Standards of Reporting Trials (CONSORT) statement[44]. Standardized monitoring of adverse events related to CMT is also needed. Studies comparing technique of CMT and standardized procedures for CeH are also needed. Finally, meta-analysis of added study may be conducted to examine the efficacy of various CMT modalities to help clinical decision making.

V. CONCLUSION

20 randomized clinical trials were included in quantitative and qualitative study. The risk of bias as well as the effect size was vary in all the trials. Comparing to Physiotherapy and Pharmacotherapy Mainly, the efficacy of CMT was proved. Although CMT was significant heterogeneous, it was generally more effective than physiotherapy, pharmacotherapy.

According to current evidence, CMT as monotherapy might have benefits on Cervicogenic Headache patient. Therefore, this treatment has the potential of non-pharmacological methods that can be used in patients who are not responding to the conventional pharmacotherapy or physiotherapy.

However, since the number of studies included and the sample sizes were small, and the methodological quality was poor, these findings should be interpreted with great caution. Further well-designed studies need to be conducted to confirm these results.

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