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Auricular acupressure is an alternative in treating constipation in leukemia patients undergoing chemotherapy: A systematic review and meta-analysis

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ABSTRACT

Objective: Auricular acupressure (AA) therapy has been widely used in Eastern Asia and Europe to prevent constipation in leukemia patients undergoing chemotherapy. The aim of this systematic review was to review data from randomized controlled trials (RCTs) of auricular acupressure therapy for preventing constipation in leukemia patients undergoing chemotherapy.

Methods: Databases that were searched from their inception until August 2017 included: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, as well as four Chinese databases [Chinese BioMedical Database, China National Knowledge Infrastructure, Wan-Fang Data, and the Chinese WeiPu Database]. In this systematic review, only RCTs that were related to the effects of auricular acupressure therapy on preventing constipation in leukemia patients undergoing chemotherapy were included. Study selection, data extraction, and validation were performed independently by two reviewers. Quantitative analyses of RCTs were performed using RevMan 5.3 software, and cochrane criteria for risk-of-bias were used to assess the methodological quality of the trials.

Results: A total of 5 RCTs met the inclusion criteria, and most were of low methodological quality. Participants in the AA plus routine care group showed significantly greater improvements in the Bristol Stool Form (BSF) [MD = 0.55, 95% CI (0.39, 0.71), $p < 0.01$] with low heterogeneity ($Chi^2 = 5.01$, $p = 0.29$, $I^2 = 20\%$). Moreover, when compared with routine care alone, meta-analysis of three RCTs indicated favorable statistically significant effects of AA plus routine care on the Constipation Assessment Scale (CAS) [MD = -1.51, 95% CI (−1.89, −1.14), $p < 0.01$] with low heterogeneity ($Chi^2 = 1.63$, $p = 0.44$, $I^2 = 0\%$). Furthermore, when compared with routine care alone, meta-analysis of two RCTs demonstrated statistically significant effects of AA plus routine care on the Patient Assessment of Constipation–Quality Of Life (PAC-QOL) [MD = -1.28, 95% CI (−1.44, −1.13), $p < 0.01$], with low heterogeneity ($Chi^2 = 0.19$, $p = 0.67$, $I^2 = 0\%$).

Conclusion: Taken together, as a potential safety therapy, only weak evidence supported the hypothesis that AA effectively prevented constipation in leukemia patients undergoing chemotherapy.

Contents

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1. Introduction

Constipation is a common health-related issue and a common side effect in leukemia patients who undergo chemotherapy. According to a recent study, the incidence of constipation among leukemia patients receiving chemotherapy is relatively high (50%–80%), and this risk is still on the rise [1]. In leukemia patients who undergo chemotherapy, constipation may result in loss of appetite, abdominal distension accompanied by abrupt abdominal pain, hemorrhoids, and rectal tearing [2]. Moreover, untreated constipation may progress to fecal impaction, intestinal obstruction, and ultimately sepsis [3]. Furthermore, chemotherapy-induced constipation may impair a patients' normal quality of life and result in severe psychological symptoms, including anxiety and stress [4]. Therefore, prevention of constipation among leukemia patients undergoing chemotherapy is of utmost importance.

Recent studies have recommended that administration of both oral and/or rectal laxatives may have beneficial effects on managing chronic constipation [4]. However, leukemia patients receiving chemotherapy usually require additional interventions to alleviate constipation-related symptoms [5]. Moreover, these interventions are frequently associated with undesired side effects, and increase the risk of serious adverse events (AEs), including electrolyte and mineral imbalances, severe dehydration, and laxative dependence [6]. Therefore, patients receiving chemotherapy in Eastern Asia often tend to seek complementary and alternative medicine (CAM) therapies to help managing their constipation [7].

Auricular acupressure (AA) is a major integral part of CAM. It has been described as a technique that involves Semen vaccariae (wang bu liu xing) seeds, Semen raphani (lai fu) seeds, Semen sinapis Albae (bai jie) seeds, or magnetic pellets with an adhesive tape on certain acupuncture points of the ears [8]. In 1990, AA was considered a type of microacupuncture that may have beneficial effects on the holistic human system [9]. Thus, therapeutic effects were achieved by stimulating specific acupuncture points in the ear that were connected to specific organs or systems of the body. AA has been systematically applied since Nogier discovered the auricular microsystem in 1957 [11]. Various neurophysiological connections exist between auricular reflex points and the autonomic and central nervous system Thus, groups of pluripotent cells contain information from the entire autonomic and central nervous system and attempt to create regional organizational centers representing different parts of the body [12]. In 1998, a USA scholar, Choy, discovered that application of ear clips to the tragus may induce significant changes in the gastrointestinal peristalsis. It was reported that the frequency of peristalsis was changed by clips on the ear and returned to normal when the clips were taken off [13]. Thus, the ears are the closest organs to the brain, and the application of AA in auricular reflex points associated with gastrointestinal function may have beneficial effects on alleviating constipation-related symptoms [14]. In addition, Western neurophysiological mechanisms have revealed that pathological changes in peripheral tissue eventually leads to dysfunctional neural firing patterns in corresponding neural microcircuits in both the brain and spinal cord [15]. Organization of the connections between peripheral nerves and the central nervous system was controlled by sites in the sensory thalamus. Stimulation of acupuncture points may serve to suppress auricular branches of the vagus nerve in the sensory thalamus, thereby raising the levels of neurotransmitters, both of which increase smooth muscle tone in the gastric wall and reduce constipation [16–21].

A bibliometrics analysis of papers published from 1994 to 2012 in China showed that AA has been widely used in preventing various chemotherapy-induced side effects, including constipation [22]. In the past, numerous systematic reviews have focused on the effects of AA on insomnia [23], postoperative pain [24], and *in vitro* fertilization [25]. Moreover, Cheng et al. summarized currently available evidence to examine the effect of AA on several types of diseases [38]. However, in this review, the author only included two RCTs to evaluate the effect of AA on preventing constipation in leukemia patients undergoing chemotherapy [26]. Therefore, the aim of the current study was to update and critically evaluate evidence from RCTs that have investigated the efficacy and safety of AA in preventing constipation in leukemia patients undergoing chemotherapy.

2. Materials and methods

2.1. Study registration

In our study, the reporting guidelines as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist were followed [27]. Moreover, the protocol of this systematic review has been registered in PROSPERO (Registration Number: CRD42017067880).

2.2. Data sources

The following databases were searched from their inception until August 2017: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Chinese BioMedical Database, China National Knowledge Infrastructure, Wan-Fang Data, Chinese WeiPu Database. Search strategies were based on the guidance of the Cochrane handbook and are presented in *Online supplementary A*. Search terms were slightly modified for other databases. o identify 'grey' literature/unpublished studies/incomplete trials, we identified relevant studies through review of the Chinese Clinical Trial Registry (http://www.chictr.org.cn/), Registry ClinicalTrials.gov (http://clinicaltrials.gov/), and WHO International Clinical Trials Registry Platform. Moreover, AA devices companies were requested to provide relevant published and unpublished data. We also searched the reference lists of review articles and/or conference articles to identified RCTs for any potential interesting titles matching the inclusion criteria of the study.

2.3. Selection of studies

In this systematic review, only RCTs related to the effects of AA in preventing constipation in leukemia patients receiving chemotherapy were included. Trials that were published in the form of dissertations were included as eligible studies. No language restrictions were imposed.

P (population): Patients diagnosed with leukemia who were over 18 years of age and undergoing chemotherapy were included in this study.

I (intervention): Studies were included if AA was used as an adjunct therapy in conjunction with routine care for preventing constipation among leukemia patients undergoing chemotherapy. In addition, studies in which other CAM therapies (e.g. acupuncture, moxibustion, massage, Chinese herbals, Chinese patent medicine) were utilized as an adjunct treatment in conjunction with the routine care were excluded.

C (comparison): A sham AA/placebo or routine care group was included as controls. Routine care involved appropriate physical exercises, dietary modification (water intake>3000 mL/d and fiber consumption) as well as psychological interventions [28]. When leukemia patients undergoing chemotherapy presented with constipation (diagnosis according to the definitive Rome III criteria), laxatives treatments were administered [29]. Moreover, studies were excluded if treatments of the control group were not relevant to routine care or when other CAM therapies (e.g. acupuncture, moxibustion, Chinese herbals, Chinese patent medicine) were used as an adjunct treatment in conjunction with routine care.

O (outcomes): *Primary outcomes*: ① Bristol Stool Form (BSF): was an internationally used validated questionnaire to determine the patients' type of feces over time [30]. This questionnaire was classified into 7 points to identify the type of feces. Overall, 1–2 points indicated constipation, 3–4 points indicated normal feces, and 5–7 points indicated diarrhea. In general, a higher score on the respective scale indicated a softer type of feces. ② Constipation Assessment Scale (CAS): CAS score was used to assess patients with constipation in a clinical settings [31]. This questionnaire included 8 items. For each item, there were three possible response options: no constipation, some problems, and severe problems. The equivalent scores were 0, 1, and 2, respectively. The total CAS score ranged from 0 to 16 and a higher score indicated a higher degree of constipation. *Secondary outcomes:* ① Patient Assessment of Constipation–Quality Of Life (PAC-QOL): was a valid and reliable measurement containing 28 items in four dimensions (physical discomfort 4 items; worries and concerns 11 items; psychosocial discomfort 8 items; and satisfaction 5 items). Each item was rated using a five-point Likert scale from 0 (not at all) to 4 (extremely). A higher score indicated a more severe effect of constipation [32]. ② Adverse Events (AEs): The incidence and the severity of AEs from AA, the proportion of patients requiring discontinuation of AA.

2.4. Data extraction, quality, and validation

Studies were selected by two independent reviewers. In most cases, any disagreement was resolved by discussion between the two reviewers. If after discussion disagreement remained, a third reviewer was consulted before a final decision on the disagreement was taken. In addition, the full text of each included study was read by two independent reviewers who extracted relevant data based on a piloted data extraction form. From each original article, the following data was extracted: (1) Author, year, and country; (2) Diagnostic criteria and sample size; (3) Experimental interventions (different materials of AA, duration of treatment, auricular acupuncture points chosen); (4) Control Interventions (routine care interventions, types of laxatives, dose, methods of administration, and the duration of treatment); (5) Follow-up; (6) Main Outcomes; (7) AEs. The information mentioned above was summarized in a data extraction table. In addition, when the reported data were insufficient, we tried our best to retrieve the missing information from the corresponding authors. The Cochrane risk of bias tool was employed by two independent reviewers to evaluate the methodological quality of each included trial [33]. Moreover, each RCT was assessed for the following characteristics: (i) selection bias; (ii) performance bias; (iii) detection bias; (iv) attrition bias; (v) reporting bias. The terms 'Low', 'Unclear', and 'High' refereed to low, uncertain, and high risk of bias, respectively. Disagreements were resolved by discussion between the two reviewers. If consensus was not reached, the third reviewer(Zhu) was consulted for a final decision.

2.5. Quantitative data synthesis

In this review, meta-analysis was performed using software RevMan 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014.) [33]. For dichotomous data, the results are presented as risk ratio (RR) with 95% confidence intervals (CIs). For continuous data, the mean difference (MD) was included in the meta-analysis. If outcome variables were measured on different scales, standard mean differences (SMD) analysis with 95% CIs were included. In addition, in each meta-analysis, the chi-square and I^2 tests were used to evaluate statistical differences [34]. Given $I^2<50\%$ and $p>0.1$, the studies were considered homogeneous, and a fixed-effects model was applied. On the other hand, if $I^2 \geq 50\%$ and $p < 0.1$, trials were considered to be heterogeneous, and a random effects model based on Mantel-Haenszel (MH) or inverse variance (IV) statistical approach was selected [34]. If a sufficient number of studies were available (at least 10 studies), publication bias was assessed using a funnel plot [35].

3. Results

3.1. Trial flow and study characteristics

The literature search of all databases generated a total of 200 citations. After excluding duplicate manuscripts, titles, and abstract, 40 full text articles were analyzed. Of these 40 articles, 35 were excluded as not all inclusion criteria were met, resulting in 5 eligible RCTs [36–40] including 388 participants for the systematic review (Fig. 1).

The 5 included RCTs all originated in China, and had a relatively

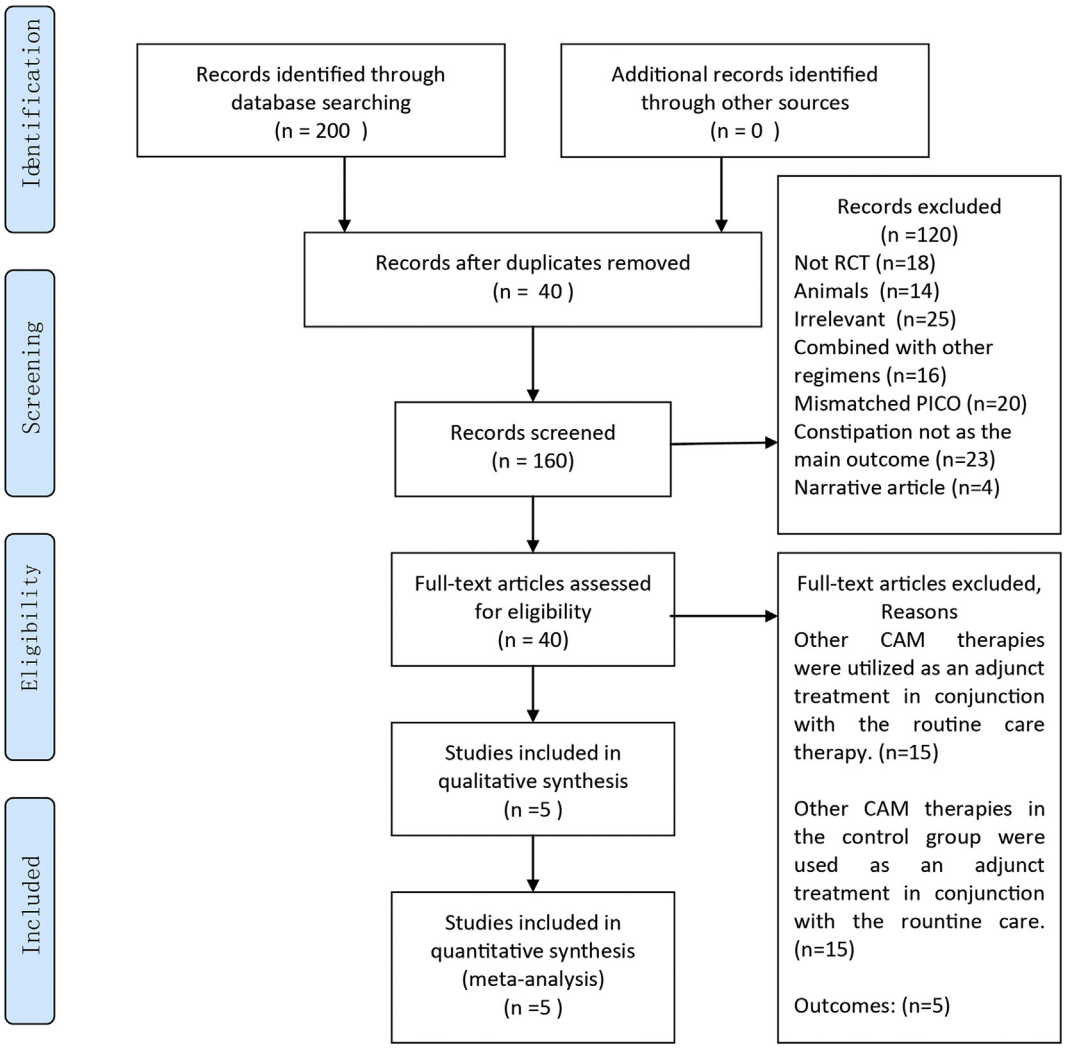

Fig. 1. Flowchart of the trial selection process.

small sample size. Moreover, all included trials compared co-intervention of AA and routine care with routine care alone as a control. Moreover, the duration and frequency of intervention was mostly 25 min and 3 times/day, respectively. The acupuncture points of AA varied according to the theory of traditional Chinese medicine (TCM) and the view of Nogier's theory for all included RCTs. Details on the 5 RCTs [36–40] included in our meta-analysis are summarized in Table 1.

3.2. Risk of bias

The Cochrane risk of bias is presented in Fig. 2. Two of the included trials [36,37] reported appropriate sequence-generation methods for randomization, whereas in the remaining trials [38–40], the methods of sequence generation were not described. One of the included trials [36] performed concealment of allocation by sealed envelopes, whereas in two RCTs [37,38] inappropriate methods were used. In the remaining trials [39,40] methods of sequence generation were not described. None of the included trials employed patient-blinding methods, whereas in 4 trials, assessor blinding was unclear [37–40]. Of the 5 included RCTs, two [36,37] stated the risk of bias for participant dropout or withdrawal. Sources of funding were shown in all included trials. Moreover, sources of direct funding were Medical Universities or Ministry of Health research foundations; these trials were considered free from the risk of bias posed by a financial conflict of interest.

3.3. Meta-analysis outcomes

3.3.1. BSF

Five RCTs [36–40] (involving 388 patients) were identified with the BSF outcome measurement. Pooled results displayed favorable significant effects of routine care combined with AA on BSF when compared with routine care alone [MD = 0.55, 95% CI (0.39, 0.71), $p < 0.01$] with low heterogeneity ($Chi^2 = 5.01$, $p = 0.29$, $I^2 = 20\%$) (Fig. 3).

3.3.2. CAS

In three RCTs [36,38,39] (involving 232 patients), CAS was measured as the outcome. The meta-analysis showed superior effects of routine care combined with AA on BSF when compared with routine care alone [MD = -1.51, 95% CI (−1.89, −1.14), $p < 0.01$] with low heterogeneity ($Chi^2 = 1.63$, $p = 0.44$, $I^2 = 0\%$) (Fig. 4).

3.3.3. PAC-QOL

In two RCTs [38,39] (involving 172 patients), PAC-QOL was used as an outcome for improvement of chemotherapy-induced constipation after treatment. Meta-analysis indicated superior effects

of routine care combined with AA on PAC-QOL when compared with routine care alone [MD = −1.28, 95% CI (−1.44, −1.13), $p < 0.01$] with low heterogeneity ($Chi^2 = 0.19$, $p = 0.67$, $I^2 = 0\%$) (Fig. 5).

3.4. Adverse events

In all included trials, only three RCTs [37–39] assessed AEs [36,40]. Several common adverse outcomes (mild discomfort or pain) from routine care combined with AA therapy group were reported in this trial.

4. Discussion

Our meta-analysis indicated that the combined use of routine care and AA was superior to routine care therapy alone regarding BSF, CAS, and PAC-QOL. Previously, Cheng, et al. summarized the effect of AA on all types of diseases [26]. Their findings were somewhat consistent with our the findings presented in the current study. The study performed by Cheng and colleagues [26] included one RCT that compared different CAM therapies. In contrast, this trial [21] was excluded from our study, based on our including criteria. To our knowledge, our inclusion criteria provided a more concrete picture on the role of AA than was presented previously. Moreover, compared to the study by Cheng et al. [26], two new RCTs [37,38] in China were included and analyzed in our study. Therefore, it is important to consider that systematic review and meta-analysis should be periodically updated as new RCTs are available.

The methodological quality of RCTs was assessed using the risk of bias assessment tool as described in the Cochrane Handbook. For adequate random sequence generation, 40% of the included studies underwent high risk of bias. For allocation concealment, group assignment was adequately concealed in 20% of included trials, whereas the remainder of the trials were given high risk of bias or unclear risk of bias. RCTs with an inadequate random sequence generation and inadequate allocation concealment may be subject to selection bias, and therefore are more likely to overestimate the results of the outcome measures [41,42]. For attrition bias, only 40% of included trials adequately reported incomplete outcome data, which may lead to attrition bias [43]. Finally, although it is a challenge to achieve subject blinding for AA, assessor blinding is still possible. Unfortunately, only one RCT included in this systematic review adopted assessor blinding, which may result in detection bias [41]. Overall, caution must be taken when attempting to generalize the results of our systematic review because of the lower quality of the included RCT.

Inclusion of a placebo or sham AA in the RCT that is comparable to the actual effects of AA may be crucial. However, of all included trials, none examined differences between sham AA and the actual effects of AA. Hence, one issue with RCTs is including a suitable sham AA control. Considering that possible effects of AA, two sham AA methods have been proposed for trials of AA (light touch at acupuncture points or the selection of sham acupuncture points), these may achieve patient blinding [44,45]. Unfortunately, in terms of the first-mentioned AA sham method; the majority of participants was able to identify the type of AA therapy they received because light touches at acupuncture points could be easily identified as an inactive treatments [46]. The main drawback of another sham AA method (the selection of sham acupuncture points) was the lack of essential TCM meridian and channel theory of AA. For example, based on the connection between auricular acupuncture points and the skin surface in TCM *zang-fun* theory, in several studies, lung auricular acupuncture points may have a positive effect on reducing pain during incisions [47]. In other words,

Table 1
Studies characteristics.

Study (author/year)	Sample size	Intervention group (regimen)	Control group (regimen)	Main outcomes	Acupuncture Points	AEs
Lee (2013) [38]	60	(A) AA (1 session = 20 min, 3 time/day, total 20 days, n = 30), plus (B).	(B) Routine care (physical exercises, dietary modification as well as psychological interventions, laxatives treatments administered if necessary), n = 30	BSF CAS	Rectum, Large intestine, Lung, and San Jiao.	n.r.
Wu (2015) [39]	56	(A) AA (1 session = 25 min, 3 time/day, total 18 days, n = 28), plus (B).	(B) Routine care (physical exercises, dietary modification as well as psychological interventions, laxatives treatments administered if necessary), n = 28	BSF	Rectum, Large intestine, Lung, San Jiao and subcortex	Mild pain.
Xie (2016) [40]	102	(A) AA (1 session = 30 min, 3 time/day, total 18 days, n = 51), plus (B).	(B) Routine care (physical exercises, dietary modificationas well as psychological interventions, laxatives treatments administered if necessary), n = 51	BSF CAS PAC-QOL	Rectum, Large intestine, Lung, San Jiao and subcortex	Mild discomfort
Zhang (2013) [41]	70	(A) AA (1 session = 30 min, 3 time/day, total 20 days, n = 35), plus (B).	(B) Routine care (physical exercises, dietary modificationas well as psychological interventions, laxatives treatments administered if necessary), n = 35	BSF CAS PAC-QOL	Rectum, Large intestine, Lung, San Jiao and subcortex	Mild pain.
Zhao (2012) [42]	100	(A) AA (1 session = 30 min, 3 time/day, total 20 days, n = 50), plus (B).	(B) Routine care (physical exercises, dietary modificationas well as psychological interventions, laxatives treatments administered if necessary), n = 50	BSF	Rectum, Large intestine, Lung, San Jiao	n.r.

AA Auricular Acupressure; Bristol Stool Form BSF; Constipation Assessment Scale CAS; n.r. not reported; Patient Assessment of Constipation–Quality Of Life PAC-QOL.

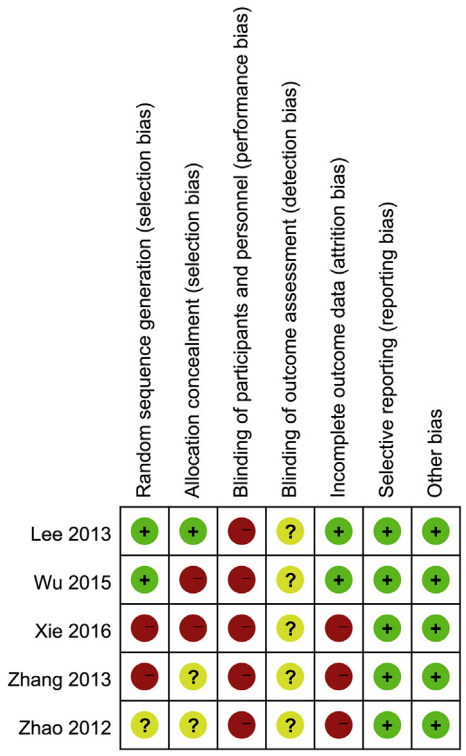

Fig. 2. Risk of bias summary: review of authors' assessment on each risk of bias item.

acupressure at a sham acupuncture point may positively or negatively affect the outcomes of an actual intervention. Thus, regarding the reliability of the method used for the current two AA shams, several discrepancies may continue to exist. In the future, adequate sham AA method should be established.

For the safety of AA in managing constipation in leukemia patients undergoing chemotherapy, except for mild discomfort or pain, no serious AA-related AEs related were reported by patients enrolled in this study. Due to the lack of a standardized stimulating intensity of AA, patients may complain of mild pain in the ear because of increasing pressing. However, in our study, no participants withdrew from the clinical trials due to AA-related AEs. Therefore, AA may be considered a relatively safe approach. Unfortunately, probable AEs related to AA such as local skin irritation and discomfort and dizziness have commonly been reported in a previous systematic review [48]. Therefore, for safety assessment, future trials should provide additional details about any AA-associated AEs.

The selection of acupuncture points may be a critical factor for influencing treatment effects. According to Wang et al., the selection of acupuncture points should be based on the TCM meridian and channel theory in China and Nogier's theory in Western Europe [49]. In our study, rectum, large intestine, lung, and San Jiao were chosen based on the principle of TCM, whereas the subcortex was chosen based on Nogier's theory. Thus, the selection of acupuncture points in our study coincided with the notion of Wang et al. Among all acupuncture points included, rectum and large intestine acupuncture points increased intestinal peristalsis, resulting in rapid passage of stool. Moreover, lung and San Jiao acupuncture points were specifically targeted at improving the flow of *Qi* and body fluids, and for distributing body fluids to moisten the intestine. The subcortex may regulate functions of the gastrointestinal tract. Therefore, stimulation of the above-mentioned acupuncture points may result in greater improvement among the subscales of constipation symptoms.

5. Limitation

Although the results are promising, this systematic review may have several important limitations. Firstly, based on the assessment of the Cochrane risk of bias, this systematic review had a high risk of bias, which may have resulted in the positive results we demonstrated. In the future, to improve the quality of the RCTs, authors are recommended to refer to the Consolidated Standards of Reporting Trials (CONSORT) statement for trials of AA interventions [50]. Secondly, the sample size of included studies was relatively

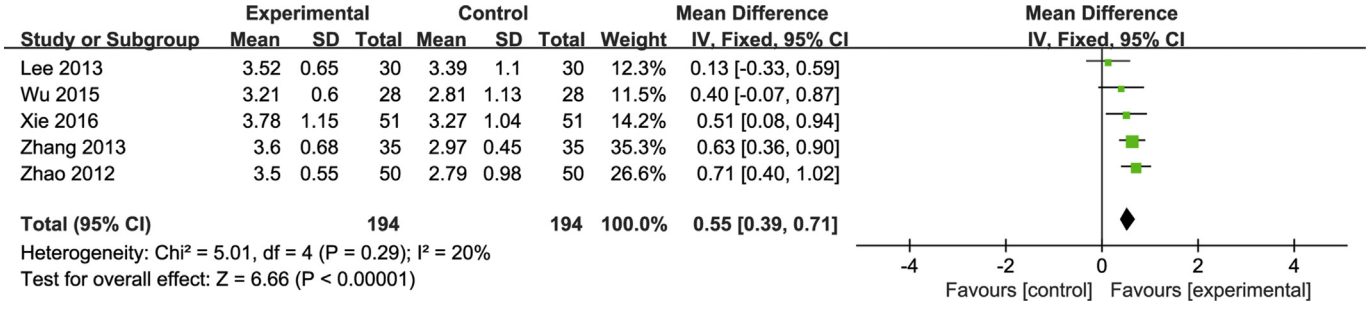

Fig. 3. Forest plots showing changes in BSF between Routine care combined with AA and Routine care alone.

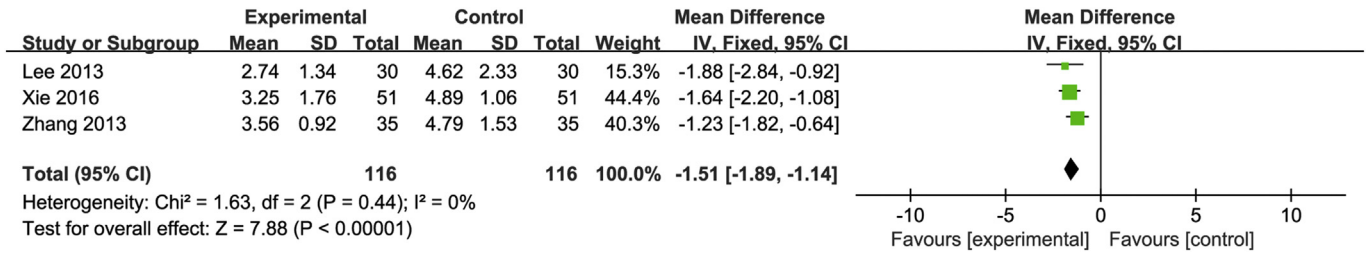

Fig. 4. Forest plots showing changes in CAS between Routine care combined with AA and Routine care alone.

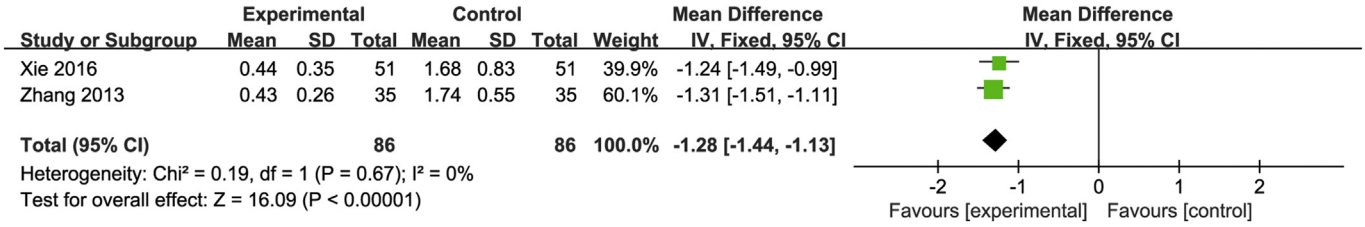

Fig. 5. Forest plots showing changes in PAC-QOL between Routine care combined with AA and Routine care alone.

small. Therefore, the power of our systematic review, which was based on small sample size effects, was more likely to be overestimated [51]. Thirdly, compared with other placebos, CAM therapy may include a larger placebo effect [52]. AA, as an important integral part of CAM, may increase the treatment effect. Moreover, AA conducted by CAM practitioners may increase physician-patient face-to face time, therefore a strong placebo effect was often found when CAM practitioners performed AA for their patients. Moreover, due to the limited number of pooled studies, it was not possible to formally test asymmetry in the funnel plot. Finally, all included RCTs originated in China, therefore the results are specific to this subset of Asian populations. In the future, large-scale, rigorously designed, randomized, placebo-controlled, double-blind trials are warranted to confirm the findings of this study.

6. Conclusion

Overall, as a potential safety therapy, only weak evidence supported the hypothesis that AA effectively prevented constipation in leukemia patients undergoing chemotherapy. In the future, more rigorous RCTs must be conducted to overcome the limitations of our existing study, and confirm the effect and safety of AA for managing constipation in leukemia patients who are undergoing chemotherapy.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ctcp.2018.03.005.

References

[1] J. Potter, F. Hami, T. Bryan, C. Quigley, Symptoms in 400 patients referred to palliative care services: prevalence and patterns, Palliat. Med. 17 (4) (2003) 310–314.
[2] P.J. Larkin, N.P. Sykes, C. Centeno, J.E. Ellershaw, F. Elsner, B. Eugene, J.R. Gootjes, M. Nabal, A. Noguera, C. Ripamonti, F. Zucco, W.W. Zuurmond, The management of constipation in palliative care: clinical practice recommendations, Palliat. Med. 22 (7) (2008) 796–807, https://doi.org/10.1177/0269216308096908.
[3] J.R. Thomas, C.F. von Gunten, Management of constipation in patients with cancer, Support Cancer Ther. 2 (1) (2004) 47–51, https://doi.org/10.3816/SCT.2004.n.022.
[4] J. Belsey, S. Greenfield, D. Candy, M. Geraint, Systematic review: impact of constipation on quality of life in adults and children, Aliment. Pharmacol. Ther. 31 (9) (2010) 938–949, https://doi.org/10.1111/j.1365-2036.2010.04273.x. Epub 2010 Feb 20.
[5] B. Candy, L. Jones, M.L. Goodman, R. Drake, A. Tookman, Laxatives or methylnaltrexone for the management of constipation in palliative care patients, Cochrane Database Syst. Rev. (1) (2011), https://doi.org/10.1002/14651858.CD003448.pub3. CD003448.
[6] J.H. Xing, E.E. Soffer, Adverse effects of laxatives, Dis. Colon Rectum 44 (8) (2001) 1201–1209.
[7] S.Y. Jeon, H.M. Jung, The effects of abdominal meridian massage on constipation among CVA patients, Taehan Kanho Hakhoe Chi 35 (1) (2005) 135–142.
[8] M. Romoli, P. Rabischong, F. Puglisi, Chapter 4-Inspection of the Outer Ear, Auricular Acupuncture Diagnosis, Churchill Livingstone, Edinburgh, 2010, pp. 55–107.
[9] WHO report of the working group on auricular nomenclature, in: W.H. Organization, World Health Organization, Lyons, France, 1990.
[11] P.F.M. Nogier, Uber die Akupunktur der Ohrmuschel, German J. Acupunct. Relat. Tech. 21 (27–28) (1957) 87–93.
[12] T. Oleson, Neurophysiological basis of auricular acupuncture, in: G. Stux, R. Hammerschlag (Eds.), Clinical Acupuncture: Scientific Basis, Springer Berlin Heidelberg, Berlin, 2001.
[13] D.S. Choy, E. Eidenschenk, Effect of tragus clips on gastric peristalsis: a pilot study, J. Altern. Compl. Med. 4 (4) (1998) 399–403.
[14] M. Yun, C.Q. Ding, Research of effects on gastric function by pressing ear points with finger, Shanghai J. Acu. Mox. 2 (3) (1987) 4–5.
[15] T.N. Lee, Thalamic neuron theory: a hypothesis concerning pain and acupuncture, Med. Hypotheses 3 (3) (1977) 113–121.
[16] B. Pomeranz, Scientific basis of acupuncture, in: G. Stux, B. Pomeranz (Eds.), Basics of Acupuncture, Springer Berlin Heidelberg, Berlin, Heidelberg, 1991, pp. 4–55.
[17] N.H. Cha, Y.K. Park, S.R. Sok, Effects of auricular acupressure therapy on stress and sleep disturbance of middle-aged women in South Korea, Holist. Nurs. Pract. 31 (2) (2017) 102–109, https://doi.org/10.1097/HNP.0000000000000197.
[18] A.-R. Kim, S.-H. Lee, J.-E. Kim, B.-Y. Kim, K.-W. Kang, S.-M. Choi, Survey on ear acupuncture usage by clinical traditional Korean medicine doctors, J. Acupunct. Meridian Stud. 5 (3) (2012) 138.
[19] Y.-t. Yang, Q.-f. Huang, Y.-f. Jia, J. Liu, X.-p. Ma, Current situation and analysis of clinical application of auricular acupoint sticking therapy, J. Acupunct. Tuina Sci. 14 (2) (2016) 141–148.
[20] J.M. Tipton, R.W. McDaniel, L. Barbour, M.P. Johnston, M. Kayne, P. LeRoy, M.L. Ripple, Putting evidence into practice: evidence-based interventions to prevent, manage, and treat chemotherapy-induced nausea and vomiting, Clin. J. Oncol. Nurs. 11 (1) (2007) 69–78.
[21] A.Z. Wang, A.W. Yang, Clinical observation on treating chemotherapy-induced constipation by auricular acupressure, Clin. J. Chin. Med. 21 (3) (2011) 22–24.
[22] T.K. Liu, Q. Wang, J. Zhou, Bibliometric analysis of current status of TCM nursing technologies application and clinical nursing care, Chin. J. Mod. Nurs. 22 (12) (2016) 22–23.
[23] Y. Lan, X. Wu, H.J. Tan, N. Wu, J.J. Xing, F.S. Wu, L.X. Zhang, F.R. Liang, Auricular acupuncture with seed or pellet attachments for primary insomnia: a systematic review and meta-analysis, BMC Compl. Altern. Med. 15 (103) (2015), https://doi.org/10.1186/s12906-015-0606-7.
[24] T.I. Usichenko, C. Lehmann, E. Ernst, Auricular acupuncture for postoperative pain control: a systematic review of randomised clinical trials, Anaesthesia 63 (12) (2008) 1343–1348, https://doi.org/10.1111/j.1365-2044.2008.05632.x.
[25] Y. Qian, X.R. Xia, H. Ochin, C. Huang, C. Gao, L. Gao, Y.G. Cui, J.Y. Liu, Y. Meng, Therapeutic effect of acupuncture on the outcomes of in vitro fertilization: a systematic review and meta-analysis, Arch. Gynecol. Obstet. 295 (3) (2017) 543–558, https://doi.org/10.1007/s00404-016-4255-y. Epub 2016 Dec 19.
[26] J.F. Cheng, C. Lo, Y.L. Tzeng, The usage of auricular acupressure in clinical nursing and evidence-based research, Hu Li Za Zhi 62 (6) (2015) 20–26, https://doi.org/10.6224/JN62.6.20.
[27] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009) e1000097, https://doi.org/10.1371/journal.pmed.1000097. Epub 2009 Jul 21.
[28] I. Mancini, E. Bruera, Constipation in advanced cancer patients, Support Care Cancer 6 (4) (1998) 356–364.
[29] D.A. Drossman, Rome III: the new criteria, Chin. J. Dig. Dis. 7 (4) (2006) 181–185.
[30] K.W. Heaton, J. Radvan, H. Cripps, R.A. Mountford, F.E. Braddon, A.O. Hughes, Defecation frequency and timing, and stool form in the general population: a prospective study, Gut 33 (6) (1992) 818–824.
[31] S.C. McMillan, F.A. Williams, Validity and reliability of the constipation assessment scale, Cancer Nurs. 12 (3) (1989) 183–188.
[32] P. Marquis, C. De La Loge, D. Dubois, A. McDermott, O. Chassany, Development and validation of the patient assessment of constipation quality of life questionnaire, Scand. J. Gastroenterol. 40 (5) (2005) 540–551.
[33] G. Higgins, Cochrane handbook for Systematic Reviews for Interventions,

Version 5.1.0, John Wiley & Sons, Ltd, West Sussex, England, 2011 updated March 2011.
[34] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (11) (2002) 1539–1558.
[35] J.A. Sterne, A.J. Sutton, J.P. Ioannidis, N. Terrin, D.R. Jones, J. Lau, J. Carpenter, G. Rucker, R.M. Harbord, C.H. Schmid, J. Tetzlaff, J.J. Deeks, J. Peters, P. Macaskill, G. Schwarzer, S. Duval, D.G. Altman, D. Moher, J.P. Higgins, Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials, BMJ 343 (2011) d4002, https://doi.org/10.1136/bmj.d4002.
[36] M. Lee, Clinical study on acupoint therapy to prevent constipation of leukemia patients after chemotherapy, Nurs. Res. 27 (2) (2013) 335–336.
[37] X.F. Wu, Y.P. Tzeng, Effect of magnetic auricular point therapy on constipation in patients with leukemia, J. Chin. Foreign Med. Res. 13 (29) (2015) 34–36.
[38] A.W. Xie, M.E. Niu, Y.Y. Chan, Effect observation for acupressure therap for chemotherapy-induced gastrointestinal reaction in adults with acute leukemia, J. Nurs. Train. 31 (6) (2016) 488–491.
[39] A.L. Zhang, L.H. Wang, J.L. Zheng, Auricular points therapy for treating constipation in leukemia patients undergoing chemotherapy, J. Nurs. 20 (8) (2013) 65–66.
[40] S.G. Zhao, A.Z. Wang, Two different nursing interventions in treating constipation in leukemia patients undergoing chemotherapy, J. Nurs. Prac. Res. 9 (21) (2012) 21–22.
[41] K.F. Schulz, I. Chalmers, R.J. Hayes, D.G. Altman, Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials, JAMA 273 (5) (1995) 408–412.
[42] E. Stack, H. Roberts, A. Ashburn, Re: allocation concealment, BMJ 344 (2012).
[43] J.F. Tierney, L.A. Stewart, Investigating patient exclusion bias in meta-analysis, Int. J. Epidemiol. 34 (1) (2005) 79–87. Epub 2004 Nov 23.
[44] C. Feng, J. Popovic, R. Kline, J. Kim, R. Matos, S. Lee, J. Bosco, Auricular acupressure in the prevention of postoperative nausea and emesis a randomized controlled trial, Bull. Hosp. Jt. Dis. 75 (2) (2017) 114–118.
[45] N.H. Cha, S.R. Sok, Effects of auricular acupressure therapy on primary dysmenorrhea for female high school students in South Korea, J. Nurs. Scholarsh. 48 (5) (2016) 508–516, https://doi.org/10.1111/jnu.12238. Epub 2016 Aug 19.
[46] C.S. Zhang, A.W. Yang, A.L. Zhang, B.H. May, C.C. Xue, Sham control methods used in ear-acupuncture/ear-acupressure randomized controlled trials: a systematic review, J. Altern. Compl. Med. 20 (3) (2014) 147–161, https://doi.org/10.1089/acm.2013.0238. Epub 2013 Oct 19.
[47] H.H. Moffet, Sham acupuncture may be as efficacious as true acupuncture: a systematic review of clinical trials, J. Altern. Compl. Med. 15 (3) (2009) 213–216, https://doi.org/10.1089/acm.2008.0356.
[48] J.Y. Tan, A. Molassiotis, T. Wang, L.K. Suen, Adverse events of auricular therapy: a systematic review, Evid Based Compl. Altern. Med. 2014 (2014) 506758, https://doi.org/10.1155/2014/506758. Epub 2014 Nov 10.
[49] L. Wang, B. Zhao, L. Zhou, Status and strategies analysis on international standardization of auricular acupuncture points, J. Tradit. Chin. Med. 33 (3) (2013) 408–412.
[50] K.F. Schulz, D.G. Altman, D. Moher, CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials, Obstet. Gynecol. 115 (5) (2010) 1063–1070, https://doi.org/10.1097/AOG.0b013e3181d9d421.
[51] M. Egger, G.D. Smith, J.A. Sterne, Uses and abuses of meta-analysis, Clin. Med. (Lond.) 1 (6) (2001) 478–484.
[52] K. Meissner, M. Fassler, G. Rucker, J. Kleijnen, A. Hrobjartsson, A. Schneider, G. Antes, K. Linde, Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis, JAMA Intern. Med. 173 (21) (2013) 1941–1951, https://doi.org/10.1001/jamainternmed.2013.10391.