REVIEW
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Effectiveness and safety of acupuncture on cancer pain: a meta-analysis

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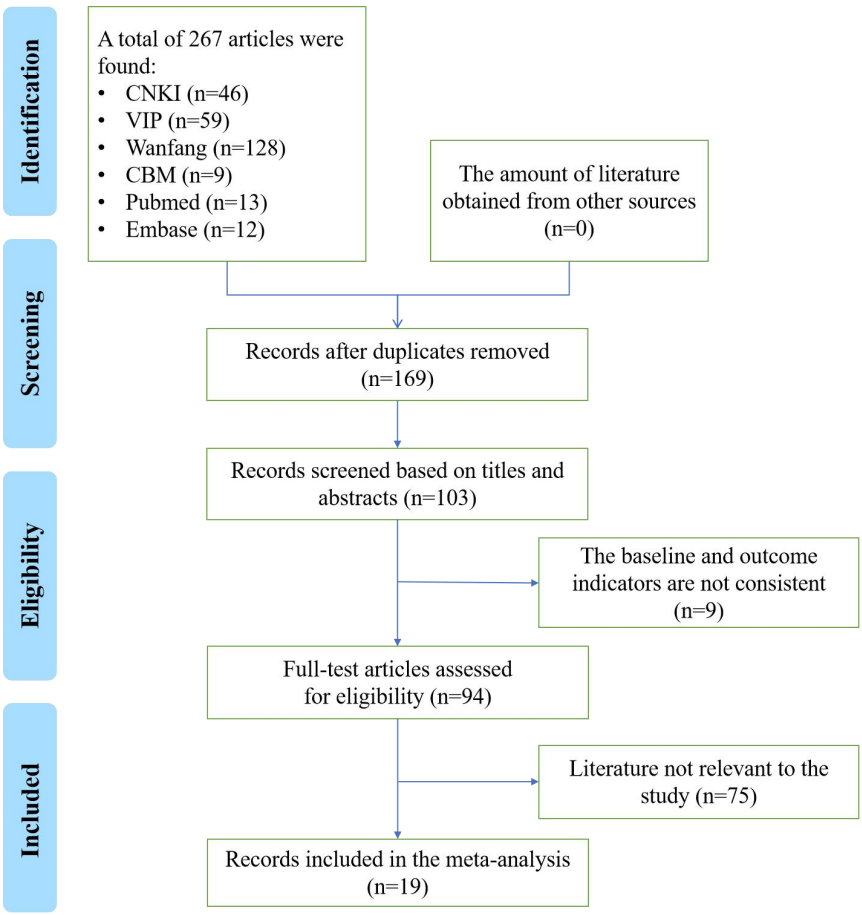
Highlights

Cancer pain is one of the most painful concomitant symptoms in patients with malignant tumors, which causes heavy physical and psychological burden to patients. Currently, the World Health Organization guidelines for the treatment of three-step cancer pain are the principal international guidelines. However, clinical opioid-related side effects, such as nausea, constipation, reduce patient dependence and often result in pain management failure. As a non-drug green therapy, acupuncture has quickly analgesic effect, no dependence, addiction, and simple and inexpensive advantages. This meta-analysis proved that acupuncture combined with opioids for cancer pain is superior to opioids alone with a lower incidence of adverse reactions.



Abstract

Objective: The aim of the study was to evaluate the efficacy of acupuncture combined with opiates in the treatment of cancer pain through the meta-analysis system. **Methods:** China national knowledge infrastructure and VIP Database for Chinese technical periodicals, China Biology Medicine, PubMed, Embase databases were searched from January 2016 to February 8, 2020 for the randomized controlled trials on the effects of acupuncture combined with opiates on cancer pain. Meta-analysis of ordered data was performed using Stata-MP64 and Review Manager 5.3 software. **Results:** A total of 242 Chinese studies and 25 English studies were retrieved. According to the inclusion and exclusion criteria, 19 literatures finally were included. The fixed effect model was used to combine the total effect values, and the combined odds ratio (OR) (95% confidence interval (CI)) was 2.981 (2.384, 3.729), suggesting that acupuncture combined with opiates was better than opiates alone in treating cancer pain (Z = 9.57, P < 0.05); the combination treatment could improve Karnofsky Performance Status score (Z = 2.48, P = 0.01), decrease Numerical Rating Scale score (Z = 2.89, P = 0.004); it also could reduce eruption pain frequency (Z = 4.32, P < 0.0001), improve the effects time (Z = 2.51, P = 0.01), and extend analgesia duration (Z = 4.33, P < 0.0001); the combination group also had lower Oxycodone dose than the control group (Z = 3.193, P = 0.001). At the same time, the incidence of adverse reactions was lower than that of the opiate treatment group alone, with a OR (95% CI) of 0.27 (0.19, 0.37) and statistical significance, Z = 8.06, P < 0.05. **Conclusion:** Acupuncture combined with opioids for cancer pain is superior to opioids alone with a lower incidence of adverse reactions.

Keywords: Acupuncture; Opioid; Eruption pain frequency; Analgesia duration; Cancer pain; Meta-analysis

***Abbreviations*:**

CNKI, China National Knowledge Infrastructure; VIP, China Science and Technology Journal Database; CBM, China Biology Medicine; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale; KPS, Karnofsky Performance Status; OR, odds ratio; CI, confidence interval.

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***Competing interests*:**

The authors declare that there is no conflict of interest.

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Background

Pain is an unpleasant and emotional feeling, with substantial or potential tissue damage. It is a subjective feeling [1], which is one of the most painful accompanying symptoms in patients with advanced cancer. 40% of patients with early and middle tumors and 90% of patients with advanced tumors suffer from moderate to severe cancerous pain, 70% of which are not effectively controlled [2].

Opioids remain the main means of pain management in patients with cancer-related pain; however, side effects associated with opioids, such as nausea, constipation, and improper use, can lead to pain management failure [3]. Therefore, many clinical methods are used to control cancer pain in order to reduce the adverse reactions caused by cancer pain.

In recent years, common acupuncture, electroacupuncture, moxibustion, auricular therapy, percutaneous electrical nerve stimulation, acupoint application have been used clinically to control cancer pain. Treatments have been proved to be easy to operate, safe and effective, with few side effects [4]. Increasing evidences have suggested that acupuncture is a different and effective method in treating cancer pain [5]. However, most of them are single-center studies with small samples, and the conclusions are not convincing. The purpose of this study was to evaluate the efficacy and safety of acupuncture combined with opioids in the treatment of cancer pain and analgesia. The full protocol of the meta-analysis and the results of the first individual patient data meta-analysis including RCTs published up to November 2015 have been published [6].

Methods

Data sources and search strategy

The following electronic databases were searched from January 2016 to February 8, 2020: China National Knowledge Infrastructure (CNKI) and China Science and Technology Journal Database (VIP), China Biology Medicine (CBM), WanFang Database, PubMed, Embase. The key search terms used were “acupuncture, electroacupuncture, ear acupuncture, wrist and ankle acupuncture”, “cancer pain”, “randomized control, RCTs” and relevant original data of the literature are extracted. Embase is presented as an example in Table 1.

Inclusion criteria

Study type. Randomized controlled trials to demonstrate the difference between the experimental group and the control group.

Study subjects. Patients had to meet the diagnostic criteria on cancer pain (Pain, defined as a sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Cancer pain or cancer-related pain is distinct from pain experienced by patients without malignancies).

Intervention measures. The control group were all given opiates, which are include oral medications, transdermal patches, and injections (all opioids were included in the study). The experimental group was treated with opiates and acupuncture which include acupuncture, electroacupuncture, ear acupuncture, wrist and ankle acupuncture, floating needle (acupuncture point is not limited, the course of treatment is more than 2 weeks).

Exclusion criteria

(1) Case reports, animal trials, basic research, personal experience, and review literature. (2) Real randomization was not implemented, studies with loopholes in the design of the study, and statistical methods were unreasonable. (3) Non-acupuncture interventions (such as physical oral study of traditional Chinese medicine, external application of traditional Chinese medicine, etc.), data are incomplete or have obvious errors; duplicate publications. (4) Baseline situation was not evaluated.

Table 1 A detailed search strategy for Embase

Search strategy		Results
#1	(acupuncture pharmacopuncture) OR ((acupuncture/exp OR acupuncture) AND (pharmacopuncture/exp OR pharmacopuncture))	626
#2	electroacupuncture/exp	6,477
#3	auricular needle	9
#4	(wrist/exp OR wrist) AND (ankle/exp OR ankle) AND (needle/exp OR needle)	94
#5	(floating/exp OR floating) AND (needle/exp OR needle)	133
#6	cancer pain/exp	20,123
#7	randomized controlled	818,077
#8	#1 OR #2 OR #3 OR #4 OR #5	7,254
#9	#6 AND #7 AND #8	12

Outcome indicators

(1) The primary observation was the pain score which was controlled within the effective Numerical Rating Scale (NRS) score was less than 3 points, and the number of bursts of pain was less than 2 in 24 hours. (2) Secondary results included pain scores which are including the NRS score and the Visual Analogue Scale (VAS) score, Karnofsky Performance Status (KPS) score, opiate dosages, onset time and duration and adverse reactions. NRS score and VAS score are methods for assessing the intensity and variation of pain. KPS score is functional status scoring, the higher the score, the better the health.

Quality evaluation

The Cochrane systematic review "bias risk assessment" tool was used to evaluate the quality of 6 indicators of the included studies: random allocation method, hidden allocation scheme, and blind method (blind method for participants/blind result evaluation), completeness of results data, selective reporting of research results, other sources of bias. In the statistical process, quality assessment is classified: 5 or more are low risk of bias; 3 to 4 are moderate risk of bias; 3 or less are risk of high bias.

Statistical analysis

The forest map generated by StataMP-64 software was used for the above description and a funnel map was drawn to evaluate the publication bias. Odds ratio (OR) was used as the statistical data for the count data, and each effect amount was a 95% confidence interval (CI). The statistics of the heterogeneity test in the forest map obey the distribution. According to the test level of $\alpha = 0.05$, if $P < 0.05$ is satisfied, there is heterogeneity between studies. At the same time, the heterogeneity of I^2 is used. Quantitative analysis (no heterogeneity: $I^2 \geq 0\%$, mild heterogeneity: $I^2 \geq 25\%$, moderate heterogeneity: $I^2 \geq 50\%$, severe heterogeneity: $I^2 \geq 75\%$), its significance. The level is set to 50% (Cochrane Handbook), that is, $I^2 \geq 50\%$, and there is greater heterogeneity between studies. In the analysis of non-heterogeneity, the combined effect amount analysis was used to select a fixed effect model, and a random effect model was used instead. Sensitivity analysis was performed if there is heterogeneity.

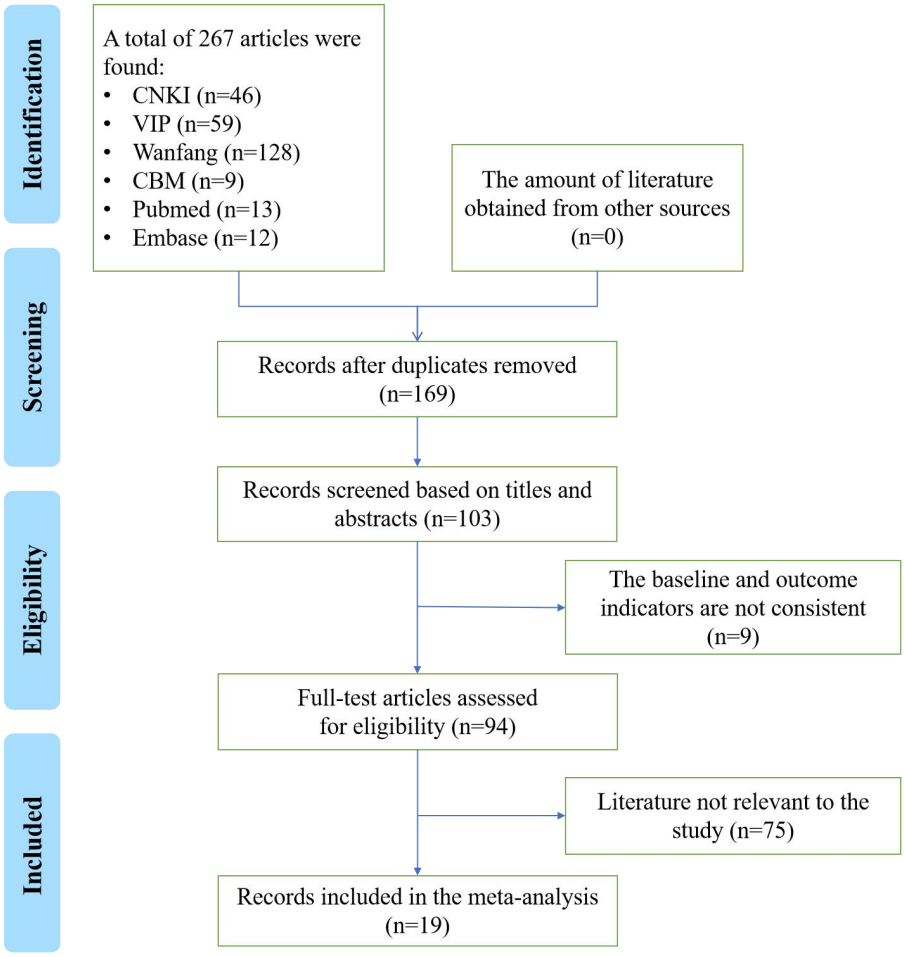

Figure 1 Study flow chart

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Results

A total of 267 related literatures were retrieved in this study (CNKI = 46 literatures; VIP = 59 literatures; Wanfang = 128 literatures; CBM = 9 literatures; PubMed = 13 literatures; Embase = 12 literatures). Combined with inclusion criteria and exclusion criteria, 95 references were excluded. In addition, 26 literatures, including review, systematic evaluation and animal experiments, were excluded; 40 literatures with inconsistent study contents or inconsistent intervention/control measures were excluded; 4 literatures without baseline information were excluded; 5 literatures with inconsistent outcome indicators were excluded; 75 literatures unrelated to the study were read; and 19 literatures were finally included. Three literatures [16, 18, 19] of them were treated with electroacupuncture, two literatures [7, 18] with fire acupuncture, five literatures [8, 13, 17, 21, 23] with wrist and ankle acupuncture, and nine literatures [7, 10–12, 14, 15, 22, 24, 25] with ordinary acupuncture.

NRS scoring method was used in 17 references and VAS scoring method was used in 2 references. All documents were from China. Blind method and allocation concealment were not used in all literatures. The study of Wang Can [16], Wang Fang [17] and Fu Yang [7] and Lu Dianrong [21] showed that the KPS score of the experimental group was higher than that of the control group after treatment, and the difference was statistically significant. The study of Wang Hui [18], Wang Can [16], Fu Yang [17], Lu Dianrong [21], Wang Ying [19] and Wu Qiulan [8] showed that the number of pain outbreaks after treatment was less in the experimental group than in the control group, and the difference was statistically significant. The study of Wang Can [16], Bai Weijie [20], Lu Dianrong [21], Hui Jianrong [10], Fan Liyong [22], Wang Ying [19], Cai Yu [24] and Wu Qiulan [8] indicated that the NRS score in the treatment group was lower than that in the control group after treatment, and the difference was statistically significant. There was no statistically significant difference between the two groups in terms of age, sex, treatment NRS, VAS, frequency of pain, KPS score, and opiate dose before treatment. The flow chart is shown in Figure 1. The baseline characteristics of all included trials are described in Table 2 and Table 3.

The Cochrane risk bias assessment tool was used to evaluate the quality of the included literature. Moderate risk was found in all 19 references (Figure 2).

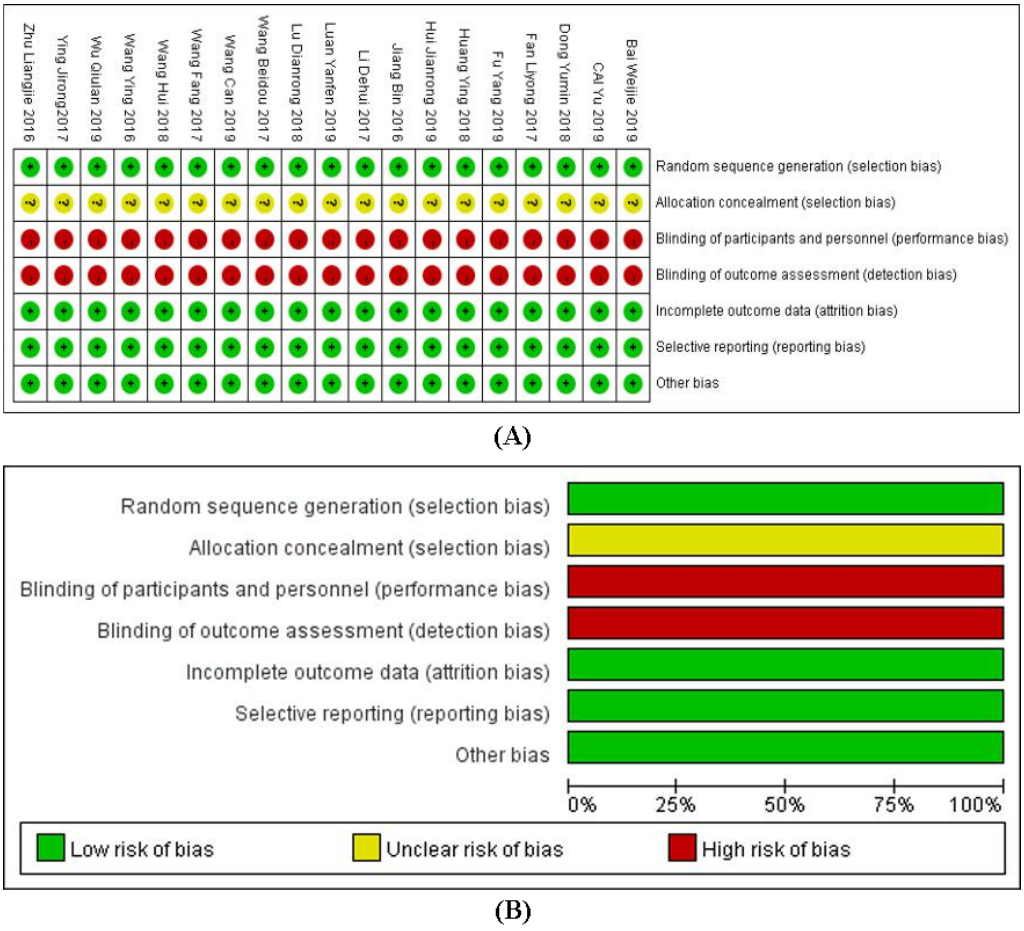

Figure 2 (A) Schematic diagram of quality assessment. **(B)** Proportion of each quality assessment.

Table 2 Characteristics of included studies

Author and year	Sample size	Gender (M/F)	Age (years)	Intervention measures	T				C				Outcomes
			T/C		CR	AR	PR	NR	CR	AR	PR	NR	
Fu Yang 2019 [7]	60	(26/14) /(24/16)	Not provided	EA + O/O	0	13	15	2	0	6	16	8	①②③④⑤⑥⑦⑧
Wu Qiulan 2019 [8]	80	(16/14) /(14/17)	55.79 ± 10.68 /55.23 ± 10.27	EA + O/O	3	19	14	4	2	15	11	12	②③⑥
Ying Jirong 2017 [9]	60	(18/12) /(20/10)	40.21 ± 1.61 /42.21 ± 1.58	A + O/O	15	13	1	1	7	9	9	5	
Hui Jianrong 2019 [10]	68	(14/20) /(15/19)	58.98 ± 13.5 /59.58 ± 13.50	A + O/O	0	5	14	15	0	7	20	7	①⑤⑦⑧
Zhu Liangjie 2016 [11]	100	(28/22) /(26/24)	47.50 ± 8.55 /46.50 ± 8.36	FA + O/O	17	20	10	3	10	10	18	12	
Li Dehui 2017 [12]	65	(17/15) /(20/13)	Not provided	WAA + O /O	7	17	7	1	1	8	16	8	⑥
Luan Yanfen 2019 [13]	35	(8/8) /(8/8)	65 ± 12 /64 ± 15	A + O/O	2	3	7	4	0	3	8	5	
Jiang Bin 2016 [14]	120	60/60	Not provided	WAA + O /O	0	33	25	2	0	15	41	4	
Wang Beidou 2017 [15]	40	20/20	Not provided	WAA + O /O	0	7	12	1	0	4	8	8	⑥
Wang Can 2019 [16]	60)	(14/16) /(15/15)	62.50 ± 10.06 /62.50 ± 10.06	WAA + O /O	0	9	13	8	0	3	9	18	①③④⑤⑥
Wang Fang 2017 [17]	80	(19/21) /(23/17)	55.12 ± 7.35 /55.26 ± 9.36	A + O/O	18	15	6	1	12	11	1	5	④⑥
Wang Hui 2018 [18]	69	(22/13) /(19/15)	58.42 ± 9.64 /55.39 ± 8.99	A + O/O	8	12	13	2	3	8	14	9	③⑥
Wang Ying 2016 [19]	50	(19/6) /(13/12)	60.52 ± 8.65 /57.92 ± 8.10	A + O/O	0	14	8	3	0	9	10	6	①③⑤⑥⑦⑧
Bai Weijie 2019 [20]	60	(16/14) /(13/17)	68.98 ± 9.83 /66.25 ± 9.32	A + O/O	0	20	5	5	0	10	14	6	①⑥
Lu Dianrong 2018 [21]	60	(16/14) /(13/17)	64.8 ± 9.4 /62.1 ± 14.7	EA + O/O	0	12	13	5	0	5	18	7	①③④⑤⑥
Fan Liyong 2017 [22]	50	(19/6) /(20/5)	Not provided	FA + O/O	9	9	5	2	4	6	6	9	①⑦⑧
Dong Yumin 2018 [23]	108	(40/14) /(43/11)	48 ± 5 /47 ± 5	A + O/O	22	18	8	6	14	15	15	10	①⑥⑦⑧
CAI Yu 2019 [24]	60	(15/15) /(16/14)	56 ± 3 /58 ± 3	WAA + O /O	0	22	4	4	0	15	8	7	②⑥
Huang Ying 2018 [25]	62	(18/13) /(20/11)	49.75 ± 2.33 /48.86 ± 0.02	A + O/O	0	26	4	1	0	17	10	4	

Note: T, treated group; C, control group; EA, electro-acupuncture; A, acupuncture; WAA, wrist ankle acupuncture; FA, fire acupuncture; O, opioids; M, male; F, female; CR, complete response; AR, apparent response; PR, partial response; NR, no response. ① Numerical Rating Scale; ② Visual Analogue Scale; ③ frequency of pain; ④ Karnofsky Performance Status; ⑤ opioid dosage; ⑥ adverse reaction; ⑦ onset time; ⑧ duration of analgesia.

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Table 3 Secondary observation data of studies included in the meta-analysis

Author and year	Sample size (M/F)	Opioid dosage	NRS (VAS) score	Frequency of pain	KPS score	Adverse reactions
				T/C		
Fu Yang 2019 [7]	60 (30/30)	Not provided	Not provided	3.60 ± 2.58/ 5.73 ± 3.87	Not provided	5/13
Wu Qiulan 2019 [8]	80 (40/40)	0.48 ± 0.17/ 0.85 ± 0.36	3.78 ± 1.37/ 4.66 ± 1.24	3.48 ± 1.53/ 6.31 ± 2.02	78.45 ± 6.90/ 72.54 ± 5.26	6/14
Ying Jirong 2017 [9]	60 (30/30)	Not provided	Not provided	Not provided	Not provided	10/17
Hui Jianrong 2019 [10]	68 (34/34)	Not provided	Not provided	Not provided	Not provided	Not provided
Zhu Liangjie 2016 [11]	100 (50/50)	Not provided	5.37 ± 0.95/ 5.89 ± 0.86	Not provided	Not provided	2/10
Li Dehui 2017 [12]	65 (32/33)	Not provided	Not provided	Not provided	Not provided	Not provided
Luan Yanfen 2019 [13]	35 (16/16)	206.19 ± 57.74/ 297.57 ± 65.16	3.0 ± 1.0/ 5.0 ± 1.0	2.9 ± 1.1/ 4.2 ± 0.8	58.6 ± 12.2/ 53.5 ± 14.1	7/9
Jiang Bin 2016 [14]	120 (60/60)	Not provided	2.09 ± 0.73/ 1.79 ± 0.70	Not provided	Not provided	35/45
Wang Beidou 2017 [15]	40 (20/20)	Not provided	Not provided	Not provided	79.0 ± 10.21/ 65.5 ± 10.50	6/12
Wang Can 2019 [16]	60 (30/30)	44.50 ± 18.16/ 56.67 ± 20.82	2.37 ± 0.76/ 2.73 ± 0.64	1.50 ± 0.68/ 1.97 ± 0.61	66.00 ± 11.02/ 65.33 ± 9.37	Not provided
Wang Fang 2017 [17]	80 (40/40)	198.523 ± 189.352/ 467.325 ± 156.354	2.90 ± 1.35/ 3.98 ± 1.46	Not provided	Not provided	Not provided
Wang Hui 2018 [18]	69 (35/34)	Not provided	4.82 ± 1.06/ 5.43 ± 1.11	Not provided	Not provided	Not provided
Wang Ying 2016 [19]	50 (25/25)	Not provided	Not provided	Not provided	Not provided	Not provided
Bai Weijie 2019 [20]	60 (30/30)	Not provided	Not provided	Not provided	Not provided	10/22
Lu Dianrong 2018 [21]	60 (30/30)	46.92 ± 34.47/ 69.60 ± 42.08	2.23 ± 0.77/ 2.66 ± 0.54	3.7 ± 3.08/ 6.00 ± 4.57	Not provided	5/20
Fan Liyong 2017 [22]	50 (25/25)	Not provided	Not provided	Not provided	Not provided	Not provided
Dong Yumin 2018 [23]	108 (54/54)	Not provided	3.01 ± 1.15/ 4.31 ± 1.99	Not provided	Not provided	14/29
CAI Yu 2019 [24]	60 (30/30)	Not provided	1.57 ± 0.73/ 2.31 ± 0.67	0.86 ± 0.72/ 1.92 ± 0.72	Not provided	5/22
Huang Ying 2018 [25]	62 (31/31)	Not provided	Not provided	Not provided	Not provided	Not provided

Note: T, treated group; C, control group; M, male; F, female; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale; KPS, Karnofsky Performance Status.

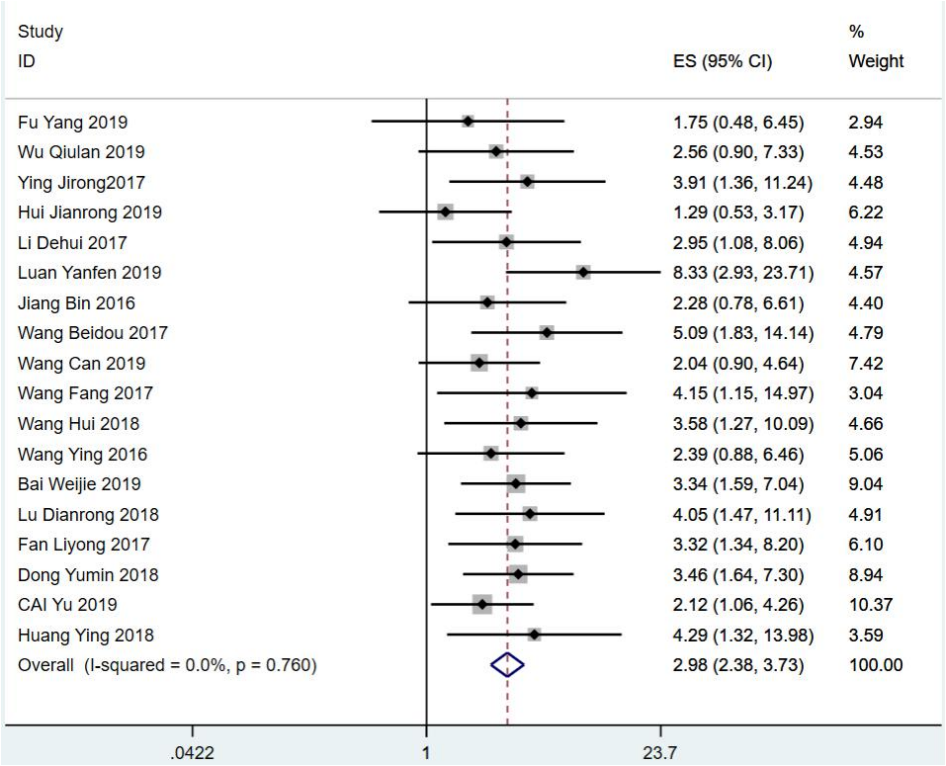

Figure 3 Forest plot of mean effect sizes for curative effect of acupuncture combined with opioid drug therapy

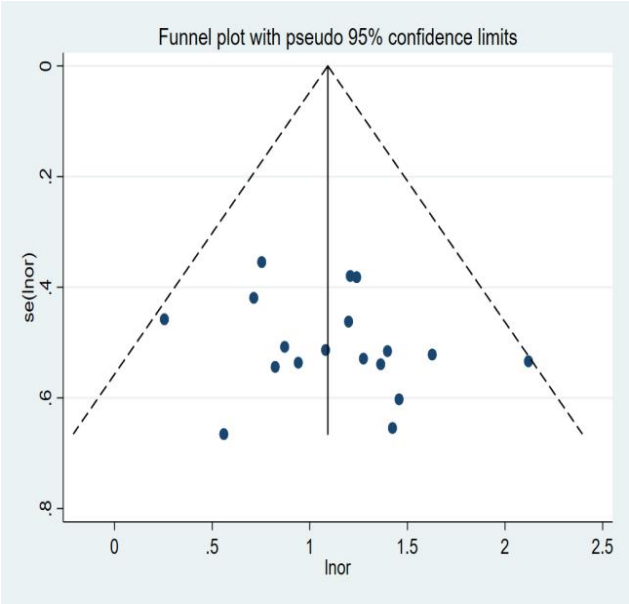

Figure 4 Funnel plot of effective rate

Meta-analysis of acupuncture for cancer pain

The 19 literatures [7–25] in this study, after the heterogeneity test, I^2 = 37.2% < 50%, P = 0.053 < 0.1, suggesting that the heterogeneity among the literature selected in this study has statistical significance. A heterogeneous search is needed. A sensitivity analysis was performed on the 19 [7–25] literatures this time, and it was found that Zhu Liangjie 2016 [11] had a greater impact on heterogeneity. After removing the study, the heterogeneity test results showed there was no heterogeneity among the remaining 18 literatures (I^2 = 0% < 50%, P = 0.76 > 0.1) (Figure 3). Then, meta-analysis was performed using fixed effects with the remaining 18 literatures. The fixed effect model was used to combine the total effect values, and the combined OR (95% CI) is 2.981 (2.384, 3.729), suggesting that acupuncture combined with opiates was better than opiates alone in treating cancer pain (Z = 9.57, P < 0.05); the combination treatment could improve KPS score (Z = 2.48, P = 0.01), decrease NRS score (Z = 2.89, P = 0.004); it also could reduce eruption pain frequency (Z = 4.32, P < 0.0001), improve the effects time (Z = 2.51, P = 0.01), and extend analgesia duration (Z = 4.33, P < 0.0001); the combination group also had lower Oxycodone dose than the control group (Z =3.193, P = 0.001). At the same time, the incidence of adverse reactions was lower than that of the opiate treatment group alone, with a OR (95% CI) of 0.27 (0.19, 0.37) and statistical significance, Z = 8.06, P < 0.05.

To investigate whether there was publication bias in this study by plotting a funnel graph, symmetry of the funnel graph means that there was no publication bias, otherwise there was publication bias (Figure 4).

Based on the begg bias test of Figure 5, P = 0.225 (> 0.05), which means that 18 literature selected in this study did not have a publication bias.

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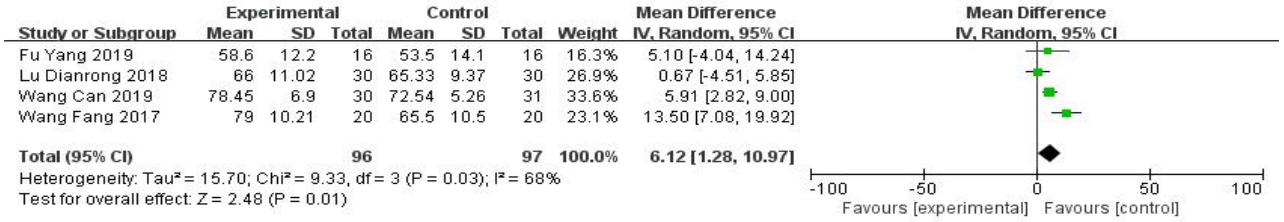

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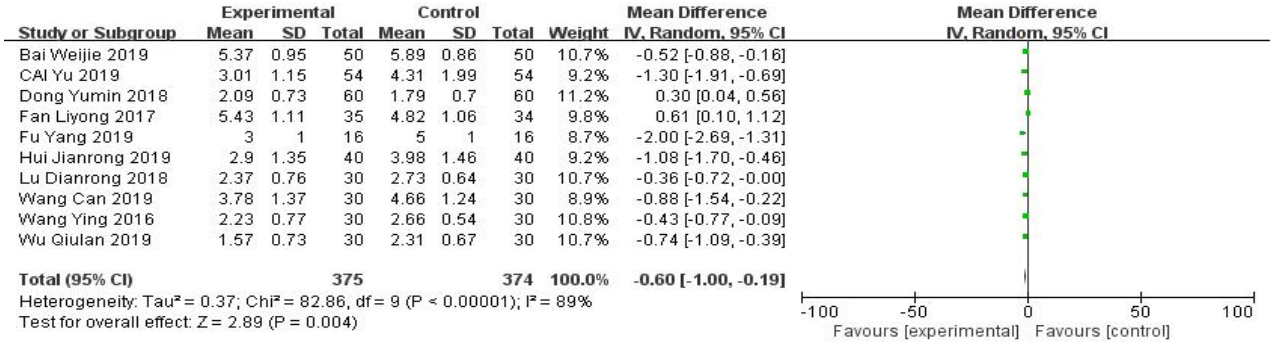

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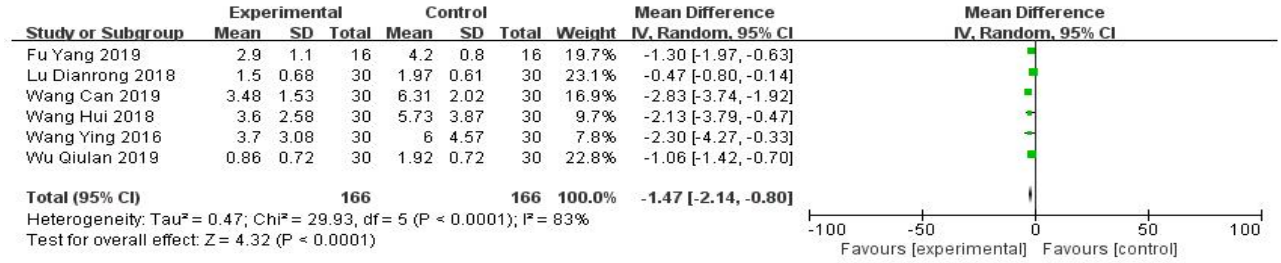

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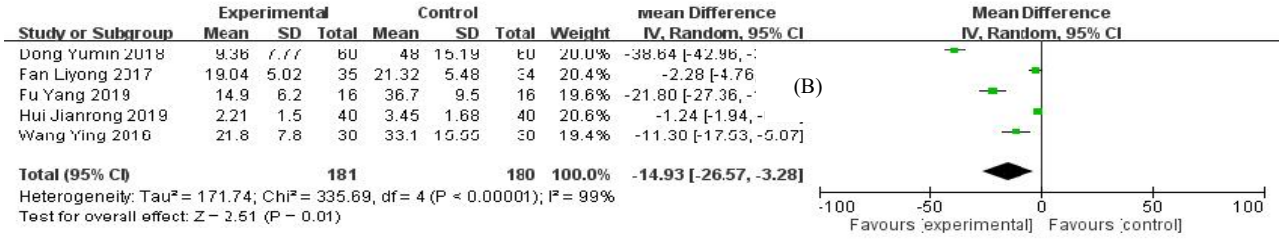

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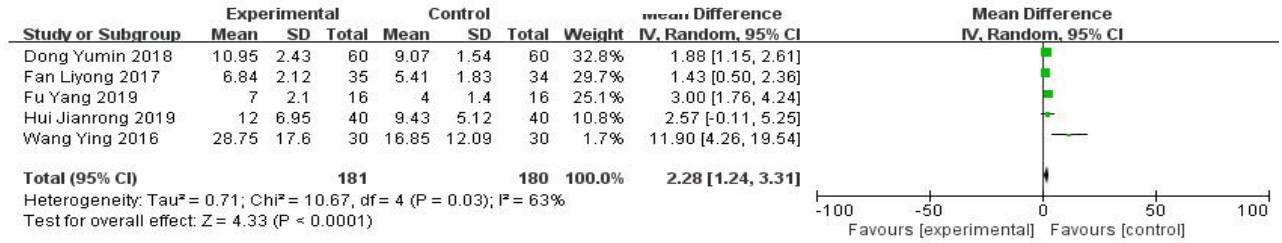

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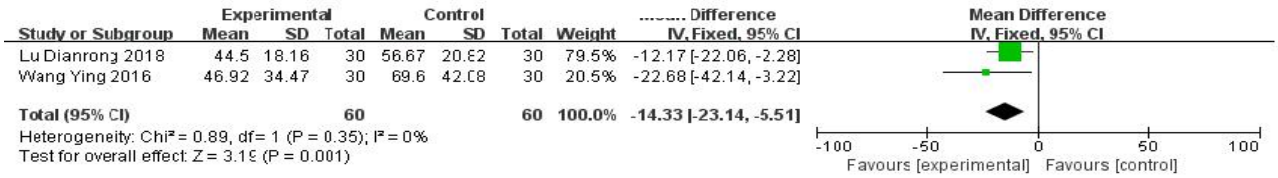

(F)

Figure 5 Forest plot of mean effect size. (A) Karnofsky Performance Status score; **(B)** Numerical Rating Scale score; **(C)** eruption pain frequency; **(D)** time to effect; **(E)** analgesia duration; **(F)** oxycodone dose.

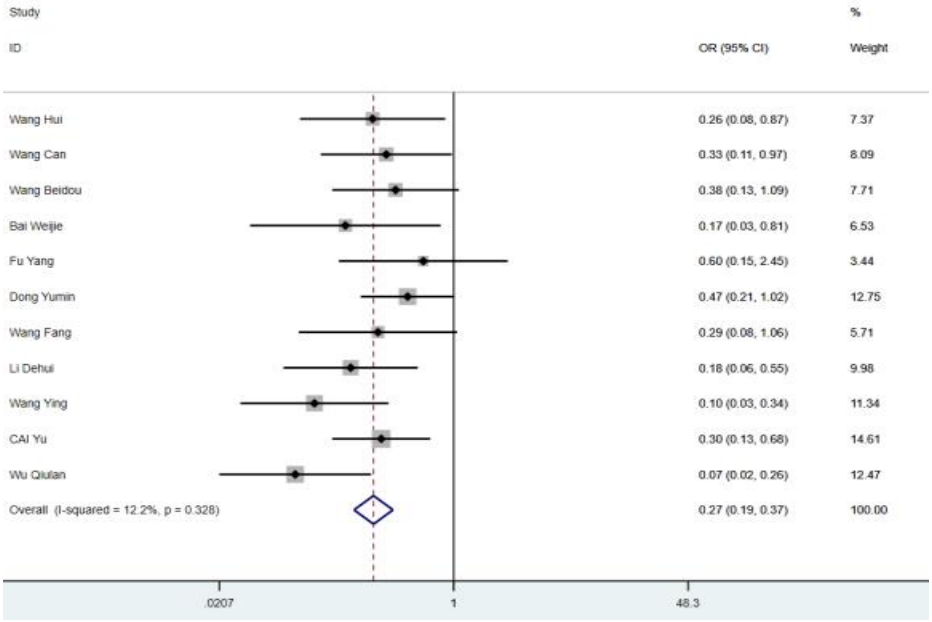

Figure 6 Forest plot of mean effect sizes for adverse reactions to acupuncture combined with opioid therapy.

Meta-analysis of adverse reactions

The 11 literatures [7–8, 15–20, 23, 24] with statistically adverse reactions were tested for heterogeneity, I^2 = 12.2% < 50%, P = 0.328, suggesting that the heterogeneity among the literature selected in this study was not statistically significant.

The OR values of the 11 studies [7–8, 15–20, 23, 24] summarized were 0.27, and the 95% CI was 0.19–0.37, which was statistically significant, Z = 8.06, P < 0.05, suggesting that acupuncture combined with opiates had fewer adverse reactions, which included lethargy, constipation, nausea and vomiting, dizziness and headache, dysuria, respiratory depression than opiates alone. The specific situation is shown in the forest plot (Figure 6).

Discussion

A total of 19 literature were included in this study. One paper was excluded from the heterogeneity test, and a total of 1216 patients were included, including 608 in the treatment group and 608 in the control group. In combination with the above, acupuncture combined with opioid therapy for cancer pain was superior to opioid therapy alone in many aspects. KPS score (Z = 2.48, P = 0.01) after treatment was higher in the experimental group than in the control group. NRS score (Z = 2.89, P = 0.004) after treatment was lower in the treatment group than in the control group, and the difference was statistically significant. The number of pain outbreaks (Z = 4.32, P < 0.0001) after treatment was less in the experimental group than in the control group. The onset time (Z =2.51, P = 0.01) and duration of analgesia (Z =4.33, P < 0.0001) were better than the control group, and the difference was statistically significant. The opioid dose (Z =3.193, P < 0.001) in the experimental group was lower than that in the control group and the difference was statistically significant. Compared with the control group, the experimental group adverse (Z = 8.06, P < 0.05) was lower.

Opioid analgesics also have certain limitations, such as long-term drug dependence, adverse reactions and strict drug management system, which restrict the clinical use of drug analgesia. These limitations lead to the unsatisfactory pain control level of community tumor patients. Traditional Chinese medicine believes that pain is caused by disorder of Qi movement of the patient, which leads to the obstruction of blood circulation. Blood circulation is obstructed in the vein, and the accumulation of toxic substances in the local area cannot be eliminated, resulting in local pain. Acupuncture has the effects of dredging meridians, regulating Qi and activating blood circulation, and relieving pain. Combined with opioids, acupuncture can learn from each other and improve the analgesic effect. This study provides a new and effective treatment idea for cancerous pain. Acupuncture combined with opiates can better provide pain management and symptom control for cancer. There are still deficiencies in the above studies, and high heterogeneity may lead to unreliable conclusions of secondary observational indicators, which need careful evaluation. The reasons may be as follows. The duration of treatment is different, leading to a large difference in opioid dosage. In addition, different statistical methods lead to differences in dosage. There

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are subjective factors in the scale score, leading to the difference in the score. Different analgesics were used in different studies, and different analgesics had different effects. None of the studies adopted blind method, and there were many subjective judgment factors. There are also some deficiencies in the conclusions of the main observed outcome indicators. Included literature did not adopt blind method and did not explain allocation concealment, which may lead to the exaggerated effect of intervention measures. In addition, not collecting unpublished literature may lead to biasing reports.

Conclusion

In conclusion, acupuncture combined with opiates for the treatment of cancer pain may have better effects and fewer adverse reactions than opiates alone. Further targeted studies are needed to obtain more reliable data support.

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