ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2016 August 26; 4(4): 77-104

Published by Baishideng Publishing Group Inc

WJMA World Journal of Meta-Analysis

A peer-reviewed, online, open-access journal of meta-analysis

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2013-2018

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WJMA World Journal of Meta-Analysis

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INDEXING/ABSTRACTING

World Journal of Meta-Analysis is now indexed in Emerging Sources Citation Index (Web of Science).

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NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Bimonthly

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http://www.wjgnet.com

PUBLICATION DATE
August 26, 2016

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World Journal of Meta-Analysis

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DOI: 10.13105/wjma.v4.i4.77

World J Meta-Anal 2016 August 26; 4(4): 77-87
ISSN 2308-3840 (online)

META-ANALYSIS

Antibiotics for eradicating meningococcal carriages: Network meta-analysis and investigation of evidence inconsistency

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Author contributions: Song F had the initial idea; Abdelhamid AS and Song F extracted data from the included trials; Song F conducted data analyses; Abdelhamid AS, Loke YK and Song F investigated causes of inconsistencies, and drafted the manuscript; Abubakar I provided clinical advice on the interpretation of results and critically commented on the manuscript; all authors approved the manuscript.

Supported by Partly the UK Medical Research Council, No. G0701607.

Conflict-of-interest statement: All authors declare no conflict of interest. The study design, data collection and interpretation have not been influenced by the funder.

Data sharing statement: All available data has been presented in the manuscript.

Manuscript source: Invited manuscript

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Received: April 25, 2016
Peer-review started: April 26, 2016
First decision: June 16, 2016
Revised: June 28, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: August 26, 2016

Abstract

AIM

To compare different antibiotics for eradicating the carriage of *Neisseria meningitidis* (*N. meningitidis*), and to investigate heterogeneity and evidence inconsistency.

METHODS

From a search of PubMed and published systematic reviews, we identified 23 trials evaluating 15 antibiotics that could be connected in a trial network. The outcome of interest is the eradication of *N. meningitidis*. We used WinBUGS to conduct random-effects, mixed treatment comparisons. Heterogeneity and evidence inconsistency was investigated by meta-regression modelling and examining characteristics of trial participants and interventions evaluated.

RESULTS

Rifampin, ciprofloxacin, minocycline, ceftriaxone, and azythromycin were statistically significantly ($P < 0.05$) more effective than placebo. The probability of being the best was 67.0% for a combination of rifampin and minocycline, 25.0% for ceftriaxone, 1.7% for azythromycin, and below 1% for the remaining regimens. Significant inconsistency between the direct and indirect estimates was observed for the comparison of rifampin and ciprofloxacin ($P < 0.01$), which may be

caused by different types of carriers and different doses of ciprofloxacin.

CONCLUSION

A range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages, and treatment choice will depend on the individual priorities of the patients and physicians. In clinical situations where complete eradication is considered to be of the utmost importance, a combination of rifampin and minocycline seems to offer the highest likelihood of success. Ceftriaxone as a single intramuscular injection is also likely to be more effective as compared with the other two antibiotics (ciprofloxacin or rifampin) recommended by the current guidelines.

Key words: Chemoprophylaxis; Antibiotics; *Nersseria meningitidis*; Meningococcal infection; Network meta-analysis

Core tip: This network meta-analysis found that a range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages. A combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than ciprofloxacin or rifampin alone. Careful investigation of significant inconsistency between direct and indirect comparison of rifampin and ciprofloxacin found that it was mainly caused by different types of carriers (persistent or any) and the varying doses of ciprofloxacin in the included trials. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in network meta-analysis.

Abdelhamid AS, Loke YK, Abubakar I, Song F. Antibiotics for eradicating meningococcal carriages: Network meta-analysis and investigation of evidence inconsistency. *World J Meta-Anal* 2016; 4(4): 77-87 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i4/77.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i4.77

INTRODUCTION

Neisseria meningitidis (*N. meningitidis*), a Gram-negative bacterium, is a normal inhabitant of the human pharynx. Transmission from person to person happens by droplets from the upper respiratory tract causing meningococcal disease; the severest forms of which are meningitis and septicaemia[1]. Meningococcal disease occurs usually sporadically or in small clusters all over the world as in the African "meningitis belt", from Ethiopia to Senegal, and also in overcrowded places or wherever large population movements exist[2].

Prevalence of meningococcal carriage varies greatly, from 8% to 25% in random samples of healthy individuals, and as high as 36% to 71% in military recruits, and shows a massive increase in overcrowded places[1]. Current public health guidelines recommend chemoprophylaxis to be offered to close contacts of cases irrespective of vaccination status[3-6]. The evidence behind these recommendations were mainly from published systematic reviews[7,8]. However, there is no definite evidence from the available direct comparison trials, as to which antibiotic is more effective in preventing secondary meningococcal disease cases[9].

With the ever increasing number of competing interventions and a shortage of direct comparison trials, methods for indirect comparison and network meta-analysis have been developed to compare different treatment options[10-13]. Because of limited evidence from direct comparison trials, we conducted a network meta-analysis of randomised controlled trials that evaluated different antibiotics for eradicating carriages of *N. meningitidis*. We also reported the methodological experience obtained from this work for appropriately investigating causes of evidence inconsistencies in network meta-analysis.

MATERIALS AND METHODS

Study eligibility and identification

We included randomised controlled trials that evaluated effects of antimicrobial interventions for the prevention of meningococcal infections. Eligible studies were selected according to the following criteria: (1) it was a randomised controlled study; (2) included participants who exposed to patients with meningococcal disease or *N. meningitidis* carriers; (3) evaluated chemoprophylaxis interventions using any antibiotic regimens; and (4) reported data on eradication of meningococcal carriage. We checked references of previous systematic reviews and conducted additional literature search to identify relevant studies for this meta-analysis. Two recently published high quality systematic reviews (with pairwise meta-analysis only) were identified, in which the literature searches were updated or conducted in June 2013[7] and in December 2013[8] respectively. We assessed the eligibility of studies included in these two reviews. To identify additional eligible studies possibly published after theses systematic reviews, one reviewer (Song F) conducted a search of PubMed in April 2016. The PubMed search used the following key words: "meningococcal" or "meningitis" combined with "chemoprevent*" or "chemoprophyl*" or antibiotic*" or antimicrobial*". In addition, the search was limited to "clinical trial" and published in the last 5 years. However, all relevant studies in the current meta-analysis could be identified from existing systematic reviews, and no new eligible studies were identified from the search of PubMed. Eventually, we included 23 trials[14-35], in which 15 different antibiotics (or combinations of antibiotics) could be connected in a network of trials (Figure 1).

Data extraction

The outcome of interest in this network meta-analysis is failure to eradicate meningococcal carriage up to one week, although only the 2-wk outcome was reported in one trial[14]. From the included studies, two independent reviewers (Asmaa S Abdelhamid and Fujian Song) extracted the following data: Antibiotics evaluated, the number of carriers, the number of carriers with failed eradication at one week after antibiotic prophylaxis, study population, carrier status, reported serogroup, susceptibility of meningococci to antibiotics, study design, adequate or inadequate allocation concealment, and open or blinded. Disagreements between the two reviewers were resolved by discussion.

Methods for mixed treatment comparison

In contrast to within-trial direct comparisons, adjusted indirect comparison is a cross-trial comparison of different treatments, based on a common treatment (for example, placebo), so that the advantage of within-trial randomisation could be partially preserved[10]. Mixed treatment comparison refers to a combination of evidence from direct comparison trials and evidence based on indirect comparisons[12]. The validity of indirect and mixed treatment comparison depends on whether some basic assumptions could be fulfilled. The basic assumptions include homogeneity assumption for conventional pair-wise meta-analysis, trial similarity assumption for adjusted indirect comparison, and consistency assumption for combining direct and indirect evidence[36]. Among these basic assumptions, heterogeneity in conventional meta-analysis and inconsistency between direct and indirect evidence can be quantitatively assessed.

Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, United Kingdom) were used to conduct the random-effects, mixed treatment comparisons based on consistency assumption[37]. The WinBUGS code for Bayesian analysis is available from a report by Dias *et al*[37,38]. We used non-informative or vague priors, and obtained results by 200000 iterations after a burn-in of 100000.

Investigating heterogeneity and causes of inconsistency

When different antibiotics could be compared both directly and indirectly, we calculated the inconsistency (Δ) between the direct and indirect evidence by the following:

$$\Delta = d_{CB} - d'_{CB}$$

$$se(\Delta) = \sqrt{Var(d_{CB}) + Var(d'_{CB})}$$

Where d_{CB} and d'_{CB} are the treatment effects (*e.g.*, log odds ratio) by direct and indirect comparison of treatment *C* and *B*; $se(\Delta)$ is the standard error of the estimated inconsistency; $Var(d_{CB})$ and $Var(d'_{CB})$ are estimated variances of the treatments effects.

We used a statistical model suggested by Cooper *et al*[39] to explore treatment by covariate interactions in the network meta-analysis. It estimates a regression coefficient by assuming a single interaction term for the relative effects of all the treatments *vs* the reference treatment (*i.e.*, placebo)[38]. The effects of the following study-level covariates were investigated: Persistent carriers *vs* any carriers, household contacts *vs* other carriers, cluster/quasi randomised controlled trials *vs* randomised trials, adequate *vs* inadequate sequence generation, and open *vs* blinded design.

We also conducted narrative investigation of causes of inconsistency, which was focused on detailed comparison of rifampin and ciprofloxacin (reasons for this will be provided later). The assessment of clinical diversity and similarity among different sets of trials is a process of identifying possible effect modifiers, which was conducted by answering the following two questions[40]. First, we examined whether there were noticeable differences in study characteristics between different sets of trials. Then, we considered whether any of the observed differences in study characteristics between trials may have modified the relative treatment effects. In this study, we examined individual trials for effect modifiers with special attention to carriage status, dose of antibiotic used and length of intervention.

There were 14 trials that compared antibiotics and placebo. Using data from these placebo-controlled trials, we produced a funnel plot to investigate risk of publication bias. Asymmetry of the funnel plot was statistically tested using Harbord's test for small-study effects[41]. All statistical analyses were conducted and checked by the corresponding author (Fujian Song) who has training and experience in statistical methods.

RESULTS

The main characteristics of the 23 trials are presented in Table 1, and data used in network meta-analyses are shown in Table 2. There are 20 two-arm trials, one three-arm trial, and two four-arm trials. The 15 antibiotics evaluated in these trials are: Placebo, rifampin, ciprofloxacin, minocycline, minocycline plus rifampin, penicillin, ampicillin, ceftriaxone, sulphadiazine, sulphadimidine, azythromycin, spectinomycin, cephalexin, "Sch29482", and coumermycin A1 (Figure 1).

Carriers were mainly from household contacts of cases (six trials), military recruits (seven trials), and students or young people (six trials). Six trials recruited heavy or persistent carriers (defined as two or more sequential positive cultures before antibiotic prophylaxis). The test of susceptibility to antibiotics was done in most of the studies. The sequence generation was inadequate or unclear in 11 trials. Blinding was performed in 12 trials, and allocation concealment was adequate in only three trials (Table 1).

There were five cluster randomised trials. We could not find empirical data on intra-cluster correlation coefficient (ICC) for the included cluster randomised trials, and therefore estimated the effective sample

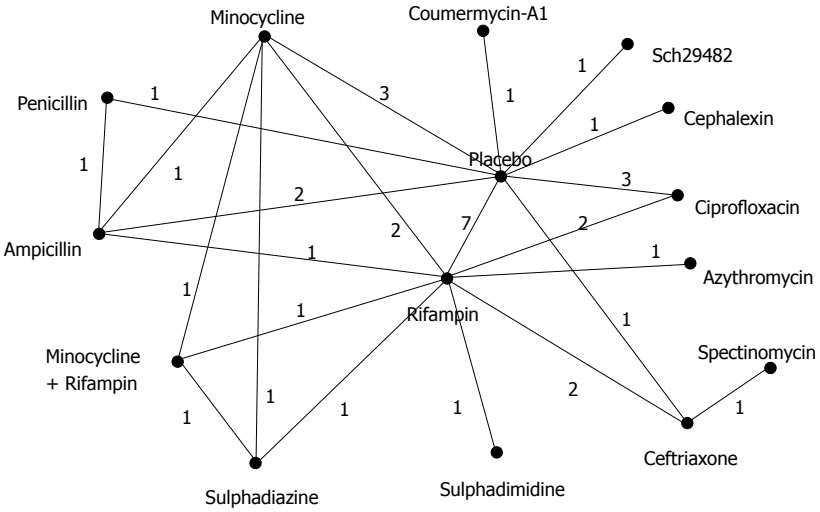

Figure 1 Network of comparisons antibiotics for preventing meningococcal infections. The lines that connect antibiotics refer the direct comparison of two antibiotics. The number beside a line is the number of trials that directly compared the two antibiotics lined by the line.

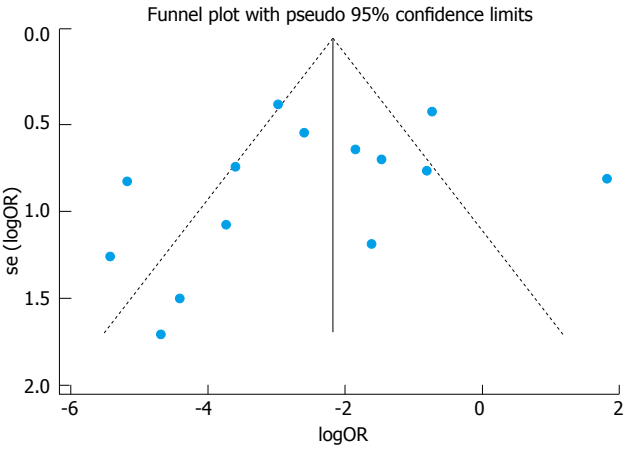

Figure 2 Funnel plot - estimated effects (log odds ratio) of antibiotics in placebo-controlled studies. Funnel plot asymmetry was not statistically significant (Harbord's test for small study effects $P = 0.600$).

sizes by assuming an ICC of 0.05[42].

Funnel plot using data from 14 placebo-controlled trials is shown in Figure 2. The funnel plot was not statistically significantly asymmetric ($P = 0.610$), indicating no concern about risk of small-study effects.

Comparison of antibiotics

The results of the network meta-analysis are shown in Table 3. Rifampin, ciprofloxacin, minocycline, ceftriaxone and azythromycin were significantly ($P < 0.05$) more effective than placebo. The probability of being the most efficacious was 67.0% for a combination of rifampin and minocycline, 25.0% for ceftriaxone, 1.7% for azythromycin, and less than 1% for the remaining antibiotics. According to evidence from the full network of trials, the combination of rifampin and minocycline was the most efficacious intervention, and ceftriaxone the second (Table 3).

The covariate effects in the network meta-analysis are shown in Table 4. Trials with persistent carriers or household contacts of cases reported significantly greater treatment effects as compared with trials of any carriers or non-household contacts of cases, while the remaining regression coefficients were not statistically significant. When the effect of persistent carrier was incorporated into the network meta-analysis, the between-study variation ($\tau = 0.434$) was much reduced as compared with the between-study variation without significant covariate adjustment ($\tau > 0.937$). Therefore, type of carriers (persistent *vs* any) may be an effect modifier[39]. However, the between-study variation was not reduced when the effect of household contacts was included in the analysis ($\tau = 0.975$).

Inconsistencies in the network meta-analysis

There is sufficient data for both direct and indirect comparisons of four pairs of antibiotics (Table 5), and the estimated inconsistencies between the direct and indirect estimates are shown in Figure 3. A statistically significant inconsistency was observed for the comparison of rifampin and ciprofloxacin. The indirect comparison based on 21 trials found that rifampin was significantly better than ciprofloxacin (OR = 0.09, 95%CI: 0.017-0.40 for failure to eradicate). In contrast, the pooling of two direct comparison trials suggested that rifampin therapy was less effective than ciprofloxacin, with a greater likelihood (non-statistically significant) of failure to eradicate (OR = 2.51, 95%CI: 0.36-15.64).

Our further investigation of causes of inconsistency was therefore focused on the comparison of rifampin and ciprofloxacin. These are also the antibiotics recommended in the current clinical guidelines. The inconsistency investigation was using data from two direct comparison trials[16,29], six placebo-controlled trials of rifampin[15,17,19,20,26,28] and three placebo-controlled trials of ciprofloxacin[24,31,33]. Figure 4 shows the results of the individual trials, with the overall estimates of direct and indirect comparisons.

While placebo controlled trials of rifampin included mostly any carriers, three placebo controlled trials of ciprofloxacin included heavy or persistent carriers (Table 1). Consequently, as shown in Figure 5, the proportion of patients with failed eradication in the placebo arm

Table 1 Main characteristics of studies included in network meta-analysis

Ref.	Antibiotics	Country and population	Carrier status	Serogroups and susceptibility	Study design	Sequence generation	Allocation concealment	Blinding
Blakebrough *et al*[14]	Rifampin: 4 × 75 mg for 0-2 yr, 4 × 150 mg for 2-4 yr, 4 × 300 mg for 5-14 yr, 4 × 600 mg for > 15 yr (bid, 2 d) Sulphadimidine: 4 × 250 mg for 0-4 yr, 4 × 500 mg for 5-14 yr, 4 × 1 g for > 15 yr (bid, 2 d)	Nigeria Household contacts	Any carriers	Group A Susceptibility tested	Cluster quasi-RCT	Inadequate	Inadequate	Open
Borgoño *et al*[15]	Rifampin: 2 × 10 mg/kg Placebo	Chile Children	Any carriers	Group unknown Susceptibility not tested	RCT	Unclear	Unclear	Double-blind
Cuevas *et al*[16]	Rifampin: 4 × 600 mg for > 18 yr, 4 × 20 mg/kg for 2-18 yr (bid, 2 d) Ciprofloxacin: 1 × 750 mg for > 18 yr, 1 × 15 mg/kg for 2-18 yr	Malawi Household contacts	Any carriers	Group A: 51% (unknown 49%) Susceptibility tested	Cluster RCT	Unclear	Unclear	Open
Deal *et al*[17]	Rifampin: 4 × 600 mg (4 d) Placebo	United States Healthy students	Heavy/ Persistent (3 positive cultures)	Group B Susceptibility tested	RCT	Adequate	Adequate	Double-blind
Deal *et al*[18]	Cephalexin: 12 × 500 mg (tid, 4 d) Placebo	United States Students	Persistent (3 positive cultures)	Group B Susceptibility tested	RCT	Adequate	Adequate	Double-blind
Deviatkina *et al*[19]	Rifampin: 4 × 300 mg (4 d) Placebo	Russia Unclear	Unknown	Group unknown Susceptibility tested	RCT	Unclear	Unclear	Open
Devine *et al*[20]	Rifampin: 4 × 600 mg (4 d) Placebo	United States Army recruits	Any carriers	Group Y: 79% Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[21]	Coumermycin A1: 14 × 50 mg (bid, 7 d) Placebo	United States Army recruits	Any carriers	Group unknown Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[22]	Minocycline: 1 × 200 mg + 9 × 100 mg (bid, 5 d) Placebo	United States Army recruits	Any carriers	Group Y: 63% Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[22]	Minocycline: 4 × 200 mg (bid, 2 d) No antibiotic	United States Army recruits	Any carriers	Group Y: Most Susceptibility tested	RCT	Adequate	Unclear	Open
Dowd *et al*[23]	Ampicillin: 30 × 500 mg (tid, 10 d) Penicillin: 30 × 462 mg (tid, 10 d) Placebo	United States Amy recruits	Any carriers	Group B and sulfadiazine-resistant	RCT	Unclear	Unclear	Double-blind
Dworzack *et al*[24]	Ciprofloxacin: 1 × 750 mg Placebo	United States Young adults	Persistent (3 positive cultures)	Group B: 41%, Z: 33% Susceptibility tested	RCT	Unclear	Unclear	Double-blind
Girgis *et al*[25]	Rifampin: 4 × 600 mg (bid, 2 d) Azithromycin: 1 × 500 mg	Egypt Nursing students	Any carriers	Group A: 37%; B: 33% Susceptibility tested	RCT	Adequate	Unclear	Open
Guttler *et al*[26]	Rifampin: 5 × 600 mg (5 d) Minocycline 10 × 100 mg (bid, 5 d) Ampicillin 10 × 500 mg (bid, 5 d) Placebo	United States Army recruits	Any carriers	Group B or C: 31% (non-groupable 67%) Susceptibility tested	Cluster RCT	Adequate	Unclear	Open
Judson *et al*[27]	Ceftriaxone: im 1 × 125 mg Spectinomycin: im 1 × 2 g	United States Patients with gonorrhoea	Any carriers	Group unknown Susceptibility tested	RCT	Unclear	Unclear	Outcome assessment blinded

Kaiser *et al*[28]	Rifampin: 4 × 600 mg for weight ⩾ 66 lb, or 4 × 300 mg for weight < 66 lb (4 d) Placebo	United States Household contacts	Any carriers	Group C: 35% Susceptibility tested	RCT	Adequate	Unclear	Open
Kaya *et al*[29]	Rifampin: 4 × 600 mg (bid, 2 d) Ciprofloxacin: 1 × 750 mg	Turkey Healthy adults	Any carriers	Group unknown Susceptibility not tested	Quasi RCT	Inadequate	Inadequate	Open
Munford *et al*[30]	Rifampin: 4 × 600 mg (bid, 2 d) Minocycline: 1 × 200 mg + 5 × 100 mg (bid, 3 d) Rifampin + Minocycline: as above Sulphadiazine: 4 × 1 g (bid, 2 d)	Brazil Household contacts	Any carriers	Group C: Most Susceptibility tested	Cluster quasi-RCT	Inadequate	Inadequate	Open
Pugsley *et al*[32]	Sch29482: 16 × 250 mg (every 6 h for 4 d) Placebo	United States	Persistent carriers (2 positive cultures)	Group Z: 36%; B: 24%	RCT	Adequate	Unclear	Double-blind
Pugsley *et al*[31]	Ciprofloxacin: 10 × 500 mg (bid, 5 d) Placebo	Young men United States	Persistent (2 positive cultures)	Susceptibility tested Group B: 79%	RCT	Adequate	Unclear	Double-blind
Renkonen *et al*[33]	Ciprofloxacin: 4 × 250 mg (bid, 2 d) Placebo	Young adults Finland	Heavy (> 100 colonies per plate)	Susceptibility tested Group B: 45%	RCT	Adequate	Adequate	Double-blind
Schwartz *et al*[34]	Rifampin: 4 × 600 mg or 4 × 10 mg/kg (bid, 2 d)	Army recruits Saudi Arabia	Any carriers	Susceptibility tested Group A	Cluster RCT	Unclear	Unclear	Open
Simmons *et al*[35]	Ceftriaxone: im 1 × 250 mg (or 125 mg for < 15 yr) Rifampin: 4 × 600 mg for adults, 4 × 5 mg/kg for children < 1 mo, and 4 × 10 mg for children > 1 mo (bid, 2 d) Ceftriaxone: im 1 × 250 mg, or 1 × 125 mg for < 12 yr	Household contacts New Zealand Household contacts	Any carriers	Susceptibility tested Group B: 53% Susceptibility tested	RCT	Unclear	Unclear	Open

im: Intramuscular; bid: Twice a day; tid: Three times a day; RCT: Randomized controlled trials.

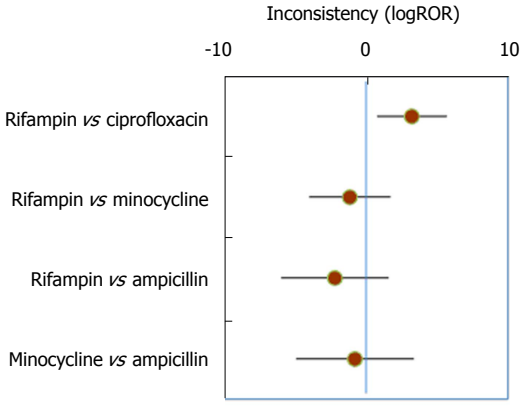

Figure 3 Inconsistencies (and 95%CIs) between direct and indirect estimates for comparisons with closed loops. logROR: 0 indicates no difference between the direct and indirect estimates.

trials of rifampin (83% *vs* 55%). If the absolute results of antibiotic interventions were not influenced by the proportion of participants with persistent carriage, trials that included persistent carriers will show greater relative treatment effects purely because of the high failure rates in the placebo group (Figure 5). Therefore, imbalanced distribution of types of carriers across different sets of trials may invalid the similarity assumption in the network meta-analysis, which raises a question whether the indirect comparison is valid in this case.

In addition, the use of ciprofloxacin in the direct comparison trials[16,29] was different from its use in the placebo-controlled trials of ciprofloxacin[24,31,33]. A single dose of ciprofloxacin was compared with multiple doses of rifampin in the two direct comparison trials, while two of the three placebo-controlled trials of ciprofloxacin compared placebo and multiple doses of ciprofloxacin (Table 1). Therefore, the effect of ciprofloxacin (with multiple doses) in the placebo-controlled trials may be enhanced as compared to the single dose in the two direct comparison trials. The eradication failure in the ciprofloxacin arm at one week was 10.5% in the direct comparison trials, as compare with only 3.0% in the placebo-controlled trials (Figure 5). The different doses of ciprofloxacin used in the direct comparison trials and in the placebo-controlled trials also contributed to the significant inconsistency observed.

DISCUSSION

According to this network meta-analysis, a range of

Table 2 Antibiotics compared and data from the included trials for network meta-analysis

Trial	Regimen	*n*	Failure to eradicate
Guttler *et al*[26]	Placebo	18 (146)	8 (65)
	Rifampin	18 (147)	2 (13)
	Minocycline	18 (147)	1 (12)
	Ampicillin	18 (147)	3 (22)
Munford *et al*[30]	Rifampin	65 (67)	6 (6)
	Sulphadiazine	79 (82)	37 (38)
	Minocycline	56 (58)	6 (6)
	Rifampin + Minocycline	59 (61)	0 (0)
Schwartz *et al*[34]	Rifampin	34 (36)	9 (9)
	Ceftriaxone	65 (68)	2 (2)
Dowd *et al*[23]	Placebo	47	26
	Penicillin	20	9
	Ampicillin	26	8
Borgoño *et al*[15]	Placebo	110	71
	Rifampin	118	10
Deal *et al*[17]	Placebo	15	13
	Rifampin	15	2
Deviatkina *et al*[19]	Placebo	43	10
	Rifampin	46	3
Devine *et al*[20]	Placebo	28	25
	Rifampin	38	7
Kaiser *et al*[28]	Placebo	6	6
	Rifampin	13	1
Dworzack *et al*[24]	Placebo	22	20
	Ciprofloxacin	24	1
Pugsley *et al*[31]	Placebo	21	14
	Ciprofloxacin	21	0
Renkonen *et al*[33]	Placebo	53	46
	Ciprofloxacin	56	2
Deal *et al*[18]	Placebo	15	14
	Cephalexin	15	11
Devine *et al*[22]	Placebo	48	42
	Minocycline	41	14
Devine *et al*[22]	Placebo	29	27
	Minocycline	53	16
Devine *et al*[21]	Placebo	39	28
	Coumermycin A1	33	31
Pugsley *et al*[32]	Placebo	29	26
	Sch29482	29	23
Cuevas *et al*[16]	Rifampin	84 (88)	3 (3)
	Ciprofloxacin	75 (79)	9 (9)
Kaya *et al*[29]	Rifampin	25	1
	Ciprofloxacin	26	2
Girgis *et al*[25]	Rifampin	59	3
	Azythromycin	60	4
Simmons *et al*[35]	Rifampin	82	4
	Ceftriaxone	100	3
Blakebrough *et al*[14]	Rifampin	46 (48)	11 (11)
	Sulphadimidine	33 (34)	33 (34)
Judson *et al*[27]	Ceftriaxone	29	0
	Spectinomycin	9	8

For cluster trials, ICC = 0.05 was assumed for estimating effective sample sizes, and original sample size and events in cluster trials are shown in brackets.

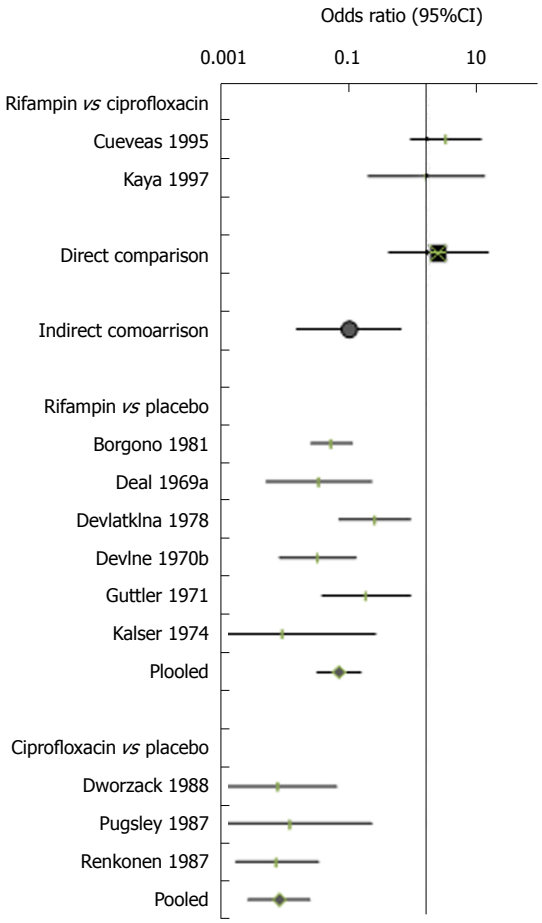

Figure 4 Rifampin *vs* ciprofloxacin for preventing meningococcal infections. The outcome is the failure to eradicate at 1 wk. Pooled direct and indirect estimates were the results of mixed treatment comparison, and other results were from DerSimonian-Laird meta-analyses.

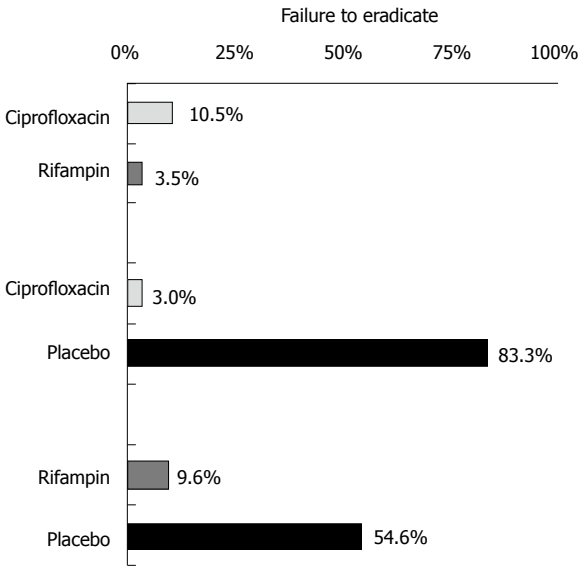

Figure 5 Proportions of failure to eradicate in individual arms of trials for the direct and indirect comparison of rifampin and ciprofloxacin.

antibiotic regimens are effective for preventing meningococcal infections in carriers. The simultaneous analysis of all randomised controlled trials that could be connected in a coherent network provided results that were not available from the conventional pair-wise meta-analysis[43]. The network meta-analysis revealed that a combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than the antibiotics (ciprofloxacin or rifampin) recommended by the current guidelines[4-6]. The network

Table 3 Results of network meta-analysis of antibiotics for preventing meningococcal infections (odds ratio of failure to eradicate)

	2 Rifampin	3 Ciprofloxacin	4 Cephalexin	5 Minocycline	6 Ampicillin	7 Penicillin	8 Ceftriaxone	9 Rifampin + minocycline	10 Azythromycin	11 Spectinomycin	12 Coumermycin A1	13 Sch29482	14 Sulphadiazine	15 Sulphadimidine
1 Placebo	0.038[a]	0.020[a]	0.274	0.058[a]	0.267	0.611	0.009[a]	0.004[a]	0.071[a]	5.971	5.524	0.498	0.487	23.17
2 Rifampin		0.53	7.201	1.536	7.028[a]	16.20[a]	0.247	0.098	1.89	156.2[a]	146.2[a]	13.15[a]	12.88[a]	601[a]
3 Ciprofloxacin			13.7	2.911	13.29[a]	30.67[a]	0.467	0.184	3.54	301.0[a]	278.0[a]	24.87[a]	24.4[a]	1174[a]
4 Cephalexin				0.214	0.980	2.26	0.035[a]	0.013[a]	0.262	22.42	20.6	1.826	1.825	91.1[a]
5 Minocycline					4.577	10.52	0.161	0.064	1.212	102.3[a]	95.57[a]	8.53	8.42[a]	396[a]
6 Ampicillin						2.291	0.035[a]	0.014[a]	0.266	22.54	20.85[a]	1.864	1.84	88.6[a]
7 Penicillin							0.015[a]	0.006[a]	0.116	9.808	9.128	0.81	0.8	39.09
8 Ceftriaxone								0.385	7.566	620[a]	597[a]	53.17[a]	52.94[a]	2493[a]
9 Rifampin + minocycline									20.15	1776[a]	1584[a]	140.2[a]	134.3[a]	7088[a]
10 Azythromycin										83.64[a]	78.9[a]	7.03	7	334[a]
11 Spectinomycin											0.924	0.082	0.084	4.032
12 Coumermycin A1												0.089	0.088	4.372
13 Sch29482													0.992	48.75
14 Sulphadiazine														47.14

[a]95%CIs did not contain zero.

meta-analysis also revealed significant inconsistency between direct and indirect estimates for the comparison of rifampin and ciprofloxacin. We investigated causes of the observed inconsistency and found that it was likely due to the following two effect modifiers: Types of carriers (persistent *vs* any), and the varying doses of ciprofloxacin.

The superior efficacy of rifampin and minocycline means it should be considered for areas where there is high degree of resistance to other agents, or in groups of patients where high rates of eradication are considered to be essential. The most efficacious regimen (rifampin and minocycline) was reported to have a significantly increased risk of adverse effects as compared to either drug alone[30]. Headache, dizziness, nausea, or vomiting were specific adverse effects noted more frequently in patients receiving the rifampin-minocycline combination. Nevertheless, patients who consider eradication of carriage to be their top priority may choose to put up with these adverse effects in order to have the best chance of treatment success.

Equally, the effectiveness of single dose intramuscular ceftriaxone, without any need to worry about patient adherence to oral regimens, makes it particularly suitable for patients when there are concerns surrounding the likelihood of the patient being able to regularly take several oral doses as prescribed. For instance, ceftriaxone would be an efficacious option in younger children who have difficulty taking tablets. Moreover, a single dose of ceftriaxone would appear to be less risky option than either ciprofloxacin or rifampin in women who are pregnant or breastfeeding. Use of ceftriaxone in both of these patient groups would be in-line with the United States CDC recommendations[3], and our network meta-analysis now provides the relevant evidence base to support this guidance.

Although the current guidelines in the United Kingdom recommend ciprofloxacin because it can be conveniently used as a single dose regimen, the results of inconsistency investigation indicate that single dose ciprofloxacin may be less effective than either multiple dose ciprofloxacin or rifampin. A regimen of multiple doses of ciprofloxacin seems preferable for persistent carriers (according to evidence from placebo-controlled trials). However, the emergence of ciprofloxacin-resistant *N. meningitidis* should also be taken into consideration[44].

Choice of optimal antibiotic strategy will be inevitably influenced by considering many factors such as cost, convenience, adherence, tolerability and bacterial resistance in a trade-off against the rate of failed eradication. For example, rifampin has been an important antibiotic agent in tuberculosis treatment, and to minimise the risk of bacterial resistance, it is not recommended as a prophylactic agent for household contacts in sub-Saharan Africa[6].

Table 4 Results of covariate effects in network meta-analysis: Regression coefficient and between study variation

Covariate	Regression coefficient, β (95%CI)	Between-study variation (τ)
Persistent carrier (1) *vs* any carriers (0)	-2.904 (-4.695 to -1.186)	0.434
Household (1) *vs* other (0)	-6.178 (-16.79 to -0.069)	0.975
Cluster/quasi RCT (1) *vs* RCT (0)	0.405 (-2.235 to 2.881)	1.082
Sequence generation inadequate (1) *vs* adequate (0)	0.461 (-1.301 to 2.014)	1.025
Open design (1) *vs* blinded (0)	0.055 (-1.877 to 1.662)	1.087

β > 0 indicating that treatment effect is smaller when the covariate exists. RCT: Randomized controlled trial.

Table 5 Results of different methods for four comparisons that provided sufficient trials for both direct and indirect comparisons

	MTC estimate		Direct estimate		Indirect estimate	
Comparison	No. of trials	OR (95%CrI)	No. of trials	OR (95%CrI)	No. of trials	OR (95%CrI)
Rifampin *vs* ciprofloxacin	23	0.52 (0.13, 1.89)	2	2.51 (0.36, 15.64)	21	0.09 (0.017, 0.40)
Rifampin *vs* minocycline	23	1.55 (0.40, 6.07)	2	0.85 (0.11, 5.59)	21	2.27 (0.28, 19.89)
Rifampin *vs* ampicillin	23	6.94 (1.21, 37.53)	1	1.62 (0.09, 29.82)	20	12.23 (1.04, 146.9)
Minocycline *vs* ampicillin	23	4.52 (0.67, 28.30)	1	3.46 (0.16, 91.10)	20	6.50 (0.41, 93.6)

MTC: Mixed treatment comparison based on all data in the network of trials.

Methodological implications

One of the main advantages of network meta-analysis is pooling of all connected trials into a coherent network of evidence. However, a study found that the inconsistency between direct and indirect evidence may be more prevalent than previously observed[45], and it has been generally accepted that causes of inconsistency in network meta-analysis should be carefully investigated[36,46-48]. In the current study, statistical meta-regression analyses found that the type of carriers (persistent *vs* any, and household contacts *vs* other) may be a cause of heterogeneity in the network meta-analysis. However, the usefulness of statistical methods for investigating causes of inconsistency is often limited because of the small number of trials, inadequate reporting of relevant variables, and modelling complexity.

The narrative investigation of causes of inconsistency is difficult for a complex network. The existence of evidence inconsistencies in a network meta-analysis does not mean that the whole network is inconsistent[46]. Therefore, we focused on the investigation of statistically significant inconsistencies. To further simplify the narrative investigation, a sub-network of trials was formed after excluding those that are only remotely connected to the target comparison.

We demonstrated that focused examination of characteristics of trial participants and interventions evaluated may reveal the clinically meaningful causes of inconsistency in network meta-analysis. The detailed examination of trial participants and interventions evaluated is similar to the investigation of heterogeneity in conventional pair-wise meta-analysis. Although the type of carriers (persistent *vs* any) can be identified by both statistical covariate analysis and narrative investigation, the difference in doses of ciprofloxacin as a possible cause of inconsistency could not be investigated by the statistical models we used. However, the narrative investigation mainly relies on subjective judgement, is restricted by available data from published studies, and a good understanding of the topic is required.

Study limitations

In order to include as many studies as possible in the trial network, we focused on eradication failure and did not consider other important outcomes such as adverse effects and new cases of meningococcal disease. Included studies were mostly conducted in 1970s or 1980s, and the most recent study was published in 2000[35]. Therefore, it is a question about whether the results of previous randomised controlled trials are applicable to the present. Although we included only randomised controlled trials, the quality of the included trials was poor, with considerable risk of bias. According to the results of meta-regression analyses (Table 4), the treatment effects were not significantly associated with whether a trial was cluster or quasi randomised, whether the sequence generation was inadequate, and whether it was blinded. In addition, publication and outcome reporting bias was possible. Funnel plot using data from placebo-controlled trials indicated that there was no statistically significant small-study effect.

Conclusion

The network meta-analysis confirms that a range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages, and treatment choice will depend on the individual priorities of the patients and physicians. In clinical situations where complete eradication is considered to be of the utmost importance, a combination of rifampin and minocycline seems to offer the highest likelihood of success. Ceftriaxone as a single intramuscular injection is also likely to be more effective as compared with the two

recommended antibiotics (ciprofloxacin or rifampin) by the current guidelines. Variation in the type of carriage and dosage regimens of ciprofloxacin may account for the observed inconsistency in the direct and indirect comparisons of rifampin and ciprofloxacin. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in network meta-analysis.

COMMENTS

Background

The current public health guidelines recommend chemoprophylaxis to be offered to close contacts of cases of meningococcal meningitis. Because of limited evidence from direct comparison trials, the authors conducted a network meta-analysis of randomised controlled trials that evaluated different antibiotics for eradicating carriages of *Neisseria meningitidis* (*N. meningitidis*).

Research frontiers

With the ever increasing number of competing interventions and a shortage of direct comparison trials, methods for indirect comparison and network meta-analysis have been widely used to compare different treatment options.

Innovations and breakthroughs

This is the first network meta-analysis to compare the efficacy of competing antibiotics for eradicating the carriage of *N. meningitidis*. Methodological experience obtained from this network meta-analysis was also reported.

Applications

For eradicating meningococcal carriages, a combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than ciprofloxacin or rifampin alone. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in all network meta-analysis.

Terminology

Network meta-analysis can be used to combine evidence from direct comparison trials and evidence based on indirect comparisons.

Peer-review

This is a well-performed network meta-analysis regarding the effects of antibiotics for eradicating carriages of *N. meningitidis*. The methodology is clear, the meta-analysis was performed well, the article was well-written, and the limitations of the study have been adequately discussed. The findings of this meta-analysis should be useful for the scientific and clinical community.

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P- Reviewer: Ayieko J, Chen GS **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Wu HL

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DOI: 10.13105/wjma.v4.i4.88

World J Meta-Anal 2016 August 26; 4(4): 88-94
ISSN 2308-3840 (online)

META-ANALYSIS

Daikenchuto for postoperative adhesive small bowel obstruction: A systematic review and meta-analysis

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Conflict-of-interest statement: The authors deny any conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: February 24, 2016
Peer-review started: February 25, 2016
First decision: April 11, 2016
Revised: May 22, 2016
Accepted: June 14, 2016
Article in press: June 16, 2016
Published online: August 26, 2016

Abstract

AIM

To assess the effectiveness of Daikenchuto for patients with postoperative adhesive small bowel obstruction (ASBO).

METHODS

A systematic search of PubMed (MEDLINE), CINAHL, the Cochrane Library and Ichushi Web was conducted, and the reference lists of review articles were hand-searched. The outcomes of interest were the incidence rate of surgery, the length of hospital days and mortality. The quality of the included studies, publication bias and between-study heterogeneity were also assessed.

RESULTS

Three randomized controlled trials (RCTs) and three retrospective cohort studies were selected for analysis. In the three RCTs, Daikenchuto significantly reduced the incidence of surgery (pOR = 0.13; 95%CI: 0.03-0.50). Similarly, Daikenchuto significantly reduced the incidence of surgery (pOR = 0.53; 95%CI: 0.32-0.87) in the three cohort studies. The length of hospital stay and mortality were not measured or described consistently.

CONCLUSION

The present meta-analysis demonstrates that administering Daikenchuto is associated with a lower incidence of surgery for patients with postoperative ASBO in the Japanese population. In order to better generalize these results, additional studies will be needed.

Key words: Herbal medicine; Kampo medicine; Postoperative adhesive small bowel obstruction; Systematic

review; Meta-analysis

Core tip: Daikenchuto, a traditional herbal medicine, is commonly used by gastroenterologists for postoperative adhesive small bowel obstruction in Japan. However, the effectiveness of Daikenchuto has not been systemically investigated. The systematic review and meta-analysis demonstrated that Daikenchuto is associated with a lower incidence of surgery for patients with postoperative adhesive bowel obstruction in the Japanese population.

Ukai T, Shikata S, Kassai R, Takemura Y. Daikenchuto for postoperative adhesive small bowel obstruction: A systematic review and meta-analysis. *World J Meta-Anal* 2016; 4(4): 88-94 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i4/88.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i4.88

INTRODUCTION

Adhesive small bowel obstruction (ASBO) is a common complication for patients with a history of abdominal surgery. ASBO accounts for up to 6% of all surgical admissions and 60% to 70% of small bowel obstruction[1,2]. Conservative management is chosen for patients with no strangulation or peritonitis, patients who underwent surgery more than six weeks before ASBO, patients with partial ASBO and patients with signs of resolution on admission[3]. Conservative management is successful in 73% to 90% of patients[4,5], but approximately one-fifth of patients later require surgery.

Essential conservative management includes decompression using a long tube or nasogastric tube intubation and intravenous fluid supplementation. According to guidelines for ASBO[3], other supplementary non-operative management options include water-soluble contrast agent administration[6], oral therapy with magnesium oxide, *Lactobacillus acidophilus* and simethicone[7], and hyperbaric oxygen therapy[8]. Water-soluble contrast agent administration, in particular, has the diagnostic value of predicting the need for surgery while the procedure itself also has therapeutic value[9].

Daikenchuto, a traditional herbal medicine, is frequently used by gastroenterologists in Japan for patients with ASBO[10] as well as chronic constipation, irritable bowel syndrome, Crohn's disease and paralytic ileus[11-14]. It comprises extract granules of processed ginger (kankyo), ginseng (ninjin) and zanthoxylum fruit (sansho). Basic research has shown several pharmacological mechanisms of Daikenchuto, including an increase in the blood flow of the intestinal tract, activation of intestinal motility, and prevention of bacterial translocation[15-17]. Recently, increasing evidence from clinical research has been accumulated[10]. However, while it is already widely used, no systematic analysis of the research has been conducted. The objective of this study was to examine the effectiveness of Daikenchuto in patients who developed postoperative ASBO.

MATERIALS AND METHODS

A systematic review was conducted, and the results were described according to the preferred reporting items for systematic reviews and meta-analyses statement[18].

Literature search

We systematically searched MEDLINE (PubMed), CINAHL, the Cochrane library and Ichushi Web, which is the largest medical article database in Japan, in November 2014. The MEDLINE search was conducted using the free-text words "Daikenchuto", "Dai-kenchu-to", "DKT" and "TJ-100". A similar literature search was conducted in the other three databases. References of review articles were also hand-searched.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the studies were randomized controlled trials (RCTs) or observational studies with exposure and control groups; (2) the participants were patients who developed postoperative ASBO; (3) daikenchuto was administered enterally; and (4) the study was performed in humans. No restriction was placed on the language. The exclusion criteria were as follows: (1) observational studies without controls; (2) Daikenchuto was administered to prevent postoperative adhesive small bowel obstruction; and (3) experimental animal research studies.

Outcome measures

The outcomes of interest were the incidence rate of surgery, the length of hospital stay, and mortality.

Quality assessment and data extraction

Two researchers (Ukai T and Shikata S) independently assessed the quality of each trial using the Critical Appraisal Skills Programme (CASP)[19] for RCTs and the Newcastle Ottawa Quality Assessment Scale (NOQAS)[20] for observational studies. The CASP asks six questions regarding the quality of RCTs. The NOQAS consists of three domains: Selection, comparability and outcome; the quality is assessed by the number of stars, with each domain having a maximum of four stars, two stars and three stars, respectively. The extracted data included the first author, year of publication, country, number of participants allocated to each group, and dosage of Daikenchuto.

Statistical analysis

The meta-analysis was conducted using the software Cochrane Collaboration Review Manager (version 5.3). All statistical analyses were performed using the Mantel-Haenszel method[21], and the summary statistics were described with odds ratios (ORs). An OR

Table 1 Characteristics of included studies

Ref.	Year	Country	Study design	Dose (g)	No. of patients with Daikenchuto (surgery: No surgery)	No. of patients without Daikenchuto (surgery: No surgery)	OR (95%CI)
Oyabu *et al*[23]	1995	Japan	RCT	15	1:27	5:20	0.15 (0.02-1.37)
Kubo *et al*[24]	1995	Japan	RCT	15	1:17	2:10	0.29 (0.02-3.67)
Itoh*et al*[25]	2002	Japan	RCT	15	5:8	10:1	0.06 (0.01-0.65)
Moriwaki *et al*[26]	1992	Japan	Retrospective cohort	15	1:23	49:154	0.14 (0.02-1.04)
Furukawa *et al*[27]	1995	Japan	Retrospective cohort	7.5-15.0	6:20	26:49	0.57 (0.20-1.58)
Yasunaga *et al*[28]	2011	Japan	Retrospective cohort	Not mentioned	20:124	28:116	0.67 (0.36-1.25)

RCT: Randomized controlled trial.

Table 2 Critical appraisal for randomized controlled trials using critical appraisal skills program

	Oyabu *et al*[23]	Kubo *et al*[24]	Itoh *et al*[25]
1 Was the assignment of patients to treatments randomized?	Y	Y	Y
2 And if so, was the randomization list concealed (blinded or masked) to those deciding on patient eligibility for the study?	Y	Y	-
3 Were all patients analysed in the groups to which they were randomized (was an "intention to treat" analysis used)?	Y	N	Y
4 Were patients in the treatment and control groups similar with respect to known prognostic factors?	Y	Y	Y
5 Were patients, clinicians and outcome assessors kept "blind" to which treatment was being received?	-	-	-
6 Was follow-up complete?	Y	Y	Y

Y: Yes; N: No.

less than one favored the intervention group, and the point estimate of the OR was considered statistically significant at the 0.05 level if the 95%CI did not include the value of one. A fixed-effects model was initially adapted for all outcome measures. We tested for homogeneity among the studies by calculating the I^2 value. I^2 can be calculated as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom[22]. We defined I^2 values of less than 25% as low heterogeneity, 25% to 50% as moderate heterogeneity and more than 50% as high heterogeneity[22]. If the hypothesis of homogeneity was rejected, a random-effects model was employed.

RESULTS

The search strategy yielded 1507 articles (Figure 1). After duplications were removed, we checked the title and abstract of the articles according to the inclusion and exclusion criteria. Full texts of the remaining articles were read, and three RCTs[23-25] and three cohort studies[26-28] were chosen based on the inclusion and exclusion criteria. Finally, the data were extracted from the studies (Table 1).

The publication year ranged from 1992 to 2011, and all research was conducted in Japan. All studies compared patients who were administered Daikenchuto with patients who were not administered Daikenchuto. The dosage of Daikenchuto was 15.0 g in four studies[23-26], 7.5-15.0 g in one study[27], and unreported in one study[28]. Daikenchuto was administered orally in one study[25], through a tube in three studies[23,24,28], or both in one study[26]. Participants were chosen regardless of the kind of abdominal surgical history in five studies[23-27], whereas only patients with a history of colorectal cancer were chosen in one study[28]. None of the included studies described the criteria of diagnosis of ASBO or pre-defined decision process for proceeding to surgery. The funnel plot of publication bias is shown in Figure 2.

Quality assessment for selected articles

Among the three RCTs, one was conducted at multiple hospitals[24], and the other two were conducted at one hospital[23,25]. In two RCTs[23,24], patients were randomly assigned using a concealed envelope, and in a third study[25], the method of assignment was not described. None of these articles mentioned the method of blinding. Patient follow-up continued until the obstruction was released and symptoms were relieved or until the patient underwent a surgery to remove the obstruction. In one trial[23], the reasons for the surgical intervention were retrospectively explained, but no explanation was provided in the other two studies[24,25]. An intention-to-treat analysis was not used in one study[24] (Table 2).

Of the three retrospective cohort studies, one was conducted using a national inpatient database using propensity score analysis[28], and both the exposure and control groups were recruited at one or several hospitals in a community[26,27]. Regarding outcome domains, the criteria for the decisions to proceed to surgery for the ASBO were not described in any of the three studies (Table 3).

Incidence of surgery in the RCTs

A total of 107 patients were included in the three

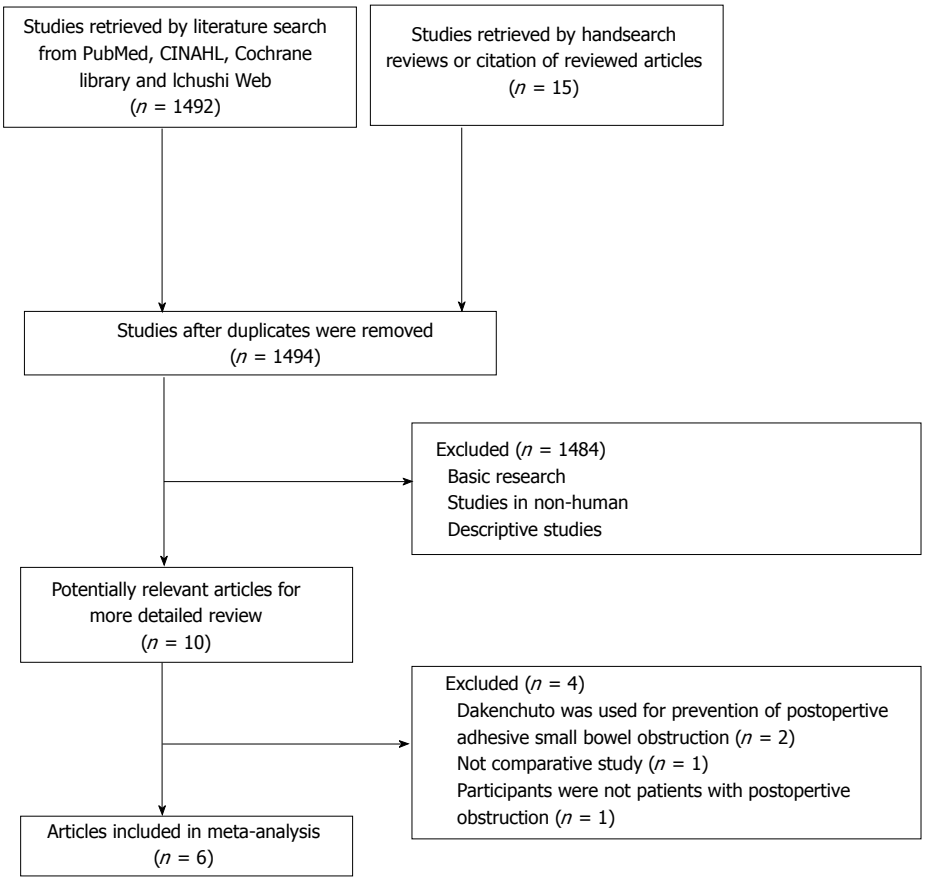

Figure 1 Search strategy according to the preferred reporting items for systematic review and meta-analyses.

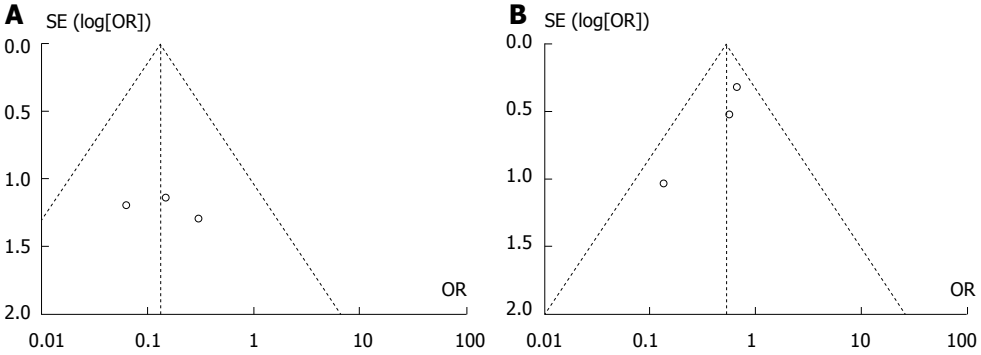

Figure 2 Funnel plot of randomized controlled trials (A) and cohort studies (B) reporting the risk of surgery in patients with postoperative adhesive small bowel obstruction given Daikenchuto. OR: Odds ratio; SE: Standard error.

RCTs (Figure 3). In the Daikenchuto group, seven of 59 (11.9%) patients eventually underwent surgery for the ASBO, whereas 17 of 48 (35.4%) patients underwent surgery in the control group. The overall OR was 0.13 (95%CI: 0.03-0.50), demonstrating statistical significance. There was no heterogeneity among the trials (I^2 = 0%).

Incidence of surgery in the cohort studies

A total of 616 patients were included in the three cohort studies (Figure 4). The incidences of surgical intervention were 27 of 194 (13.9%) in the Daikenchuto group and 103 of 422 (24.4%) in the control group. The overall OR was 0.53 (95%CI: 0.32-0.87), also demonstrating statistical significance. There was low heterogeneity among the trials (I^2 = 12%).

Other outcomes

Mortality was described in the one cohort study with a total of 288 patients[28]. The number of deaths identified was four (2.8%) in the Daikenchuto group and two (1.4%) in the control group, and this difference was not found to be significant.

Length of hospital stay was described in two studies. One RCT[27] showed that the length of the hospital stay was 5.90 d shorter (95%CI: 4.77-7.03) in the

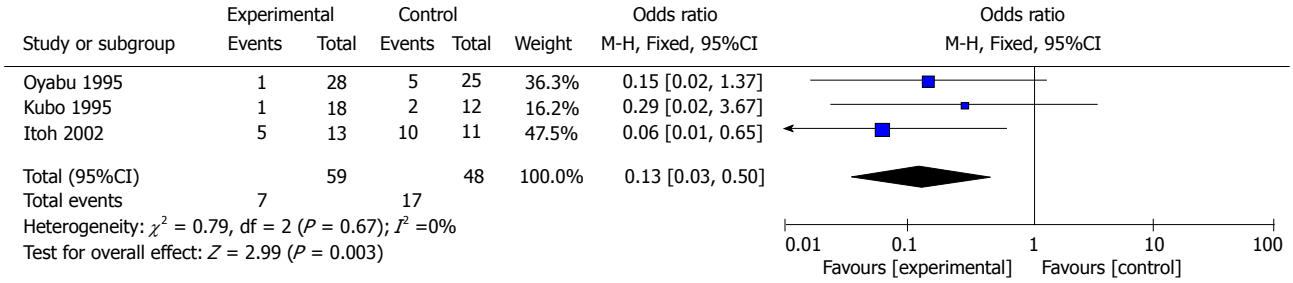

Figure 3 Effect of Daikenchuto on need for surgery for postoperative adhesive small bowel obstruction from randomized controlled trials. Boxes indicate estimated odds ratio; Diamond, summary statistic; limit lines, 95%CI. Size of the data marker corresponds to the relative weight assigned to the pooled analysis using fixed-effects model. The X-axis uses a log scale.

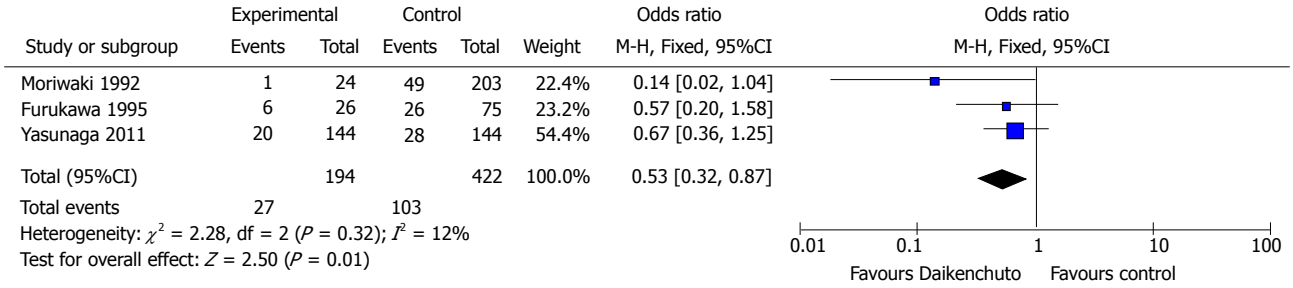

Figure 4 Effect of Daikenchuto on need for surgery for postoperative adhesive small bowel obstruction from cohort studies boxes indicate estimated odds ratio; Diamond, summary statistic; limit lines, 95%CIs. Size of the data marker corresponds to the relative weight assigned to the pooled analysis using fixed-effects model. The X-axis uses a log scale.

Table 3 Critical appraisal for cohort studies using newcastle ottawa quality assessment scale

	Moriwaki *et al*[26]	Furukawa *et al*[27]	Yasunaga *et al*[28]
Selection			
Representativeness of the exposed cohort			Y
Selection of non-exposed cohort	Y	Y	Y
Ascertainment of exposure	Y	Y	Y
Demonstration that outcome of interest was not present at start of study	Y	Y	Y
Comparability			
Comparability of cohorts on the basis of the design or analysis	Y	Y	Y
Outcome			
Assessment of outcome			
Was follow-up long enough to occur	Y	Y	Y
Adequacy of follow up of cohorts	Y	Y	Y

Y: Yes.

Daikenchuto group. Also, one cohort study[28] showed statistical significance in favor of the Daikenchuto group using Kaplan-Meier methods and log-rank test (P = 0.018).

DISCUSSION

This systematic review provides evidence from three RCTs and three cohort studies conducted in Japan concerning the effectiveness of the traditional herbal medicine Daikenchuto in reducing the risk of surgery for patients with postoperative ASBO. From the synthesized results, ASBO patients who received Daikenchuto had a significantly lower risk of surgery. The study assessed RCTs and cohort studies individually, and they provided consistent results.

Potential benefit of daikenchuto

There are several treatment options recommended in guidelines for ASBO[3]. Among the options, water-soluble contrast agent administration is highly recommended because there is robust evidence for its efficacy both in predicting a need for surgery and for preventing surgery[9]. However, despite its established efficacy, 20.8% of ASBO patients treated this way proceed to surgery[9]. Daikenchuto has widely been used in Japan and has a low risk of side effects[29], and the cost is only 145.5 JPY (US$1.25) per day. From these perspectives, Daikenchuto could be used as part of initial non-operative management adjunct to water-soluble contrast

administration. It is potentially useful for patients who have a high risk of anaphylactoid reaction to water-soluble contrast agent or patients who cannot tolerate surgery.

Traditional herbal medicine in Japan

Traditional Japanese herbal medicine is known as Kampo medicine. Kampo medicine has its roots in traditional Chinese medicine and was introduced to Japan in the middle of the sixth century. The Japanese Ministry of Health, Labour and Welfare has officially approved 212 types of Kampo medicines, and these medicines are covered by the National Health Insurance programme[30]. All certified medical doctors can prescribe both Western and Kampo medicines, and they choose the optimal one depending on the condition of the patients. Kampo medicine is referred to as an alternative medicine, but in practice, Japanese physicians use both Western medicine and Kampo medicine; in particular, Kampo medicine is commonly used for patients with medically unexplained symptoms that Western medicine often fails to solve[10]. The mechanism of the pharmacological effect is becoming clear, but more clinical research is needed before Kampo medicine will be widely adopted in other countries.

Limitations

This study has several limitations. First, the included studies have methodological problems. None of included three RCTs described the blinding of clinicians and assessors. Also, none of the included studies described the criteria of decisions of proceeding to surgery. Since the decision to proceed to surgery can be subjective, there may be bias in this outcome statistic, especially when clinicians were not blinded.

Second, the reviewed studies were conducted in Japan using Japanese populations. In three studies[23,25,26], participants were recruited at one hospital. These facts pose the question of generalizability. Thus, additional evidence is needed from patients in other countries.

Finally, all studies included compared those patients who were administered Daikenchuto and who were not. We could not find studies that compared Daikenchuto and water-soluble contrast agent. Since administering water-soluble contrast agent is the standard of care, Daikenchuto and water-soluble contrast agent should be directly compared before it is applied to clinical practice.

The traditional herbal medicine Daikenchuto significantly reduces the risk of surgery for patients with postoperative ASBO in a Japanese population. In order to better generalize these results, additional studies incorporating a broader set of outcomes and an expanded population base will be needed.

ACKNOWLEDGMENTS

We thank Alberto Gayle for his critical reading and language editing of the manuscript.

COMMENTS

Background

Adhesive small bowel obstruction (ASBO) is a common complication for patients with a history of abdominal surgery, and one fifth of them later require surgery. Daikenchuto, a traditional herbal medicine, is commonly used for postoperative adhesive small bowel obstruction, but the effectiveness of Dakenchuto in preventing surgery for patients with postoperative ASBO is not systemically assessed.

Research frontiers

Evidence in traditional herbal medicine from clinical research, as well as basic research has increasingly been accumulated. However, the evidence is not systemically collected and integrated.

Innovations and breakthroughs

In the present study, the authors demonstrated the effectiveness of Daikenchuto for preventing patients by pooling results from randomized controlled trials and cohort studies. This is the first report of meta-analysis to assess the traditional herbal medicine, Daikenchuto.

Applications

The present study allows understanding the role of Daikenchuto for patients with postoperative ASBO to prevent surgery.

Peer-review

It is a very interesting paper and a new approach to manage the adhesive small bowel obstruction.

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P- Reviewer: Fortea-Sanchis C **S- Editor**: Qi Y **L- Editor**: A
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DOI: 10.13105/wjma.v4.i4.95

World J Meta-Anal 2016 August 26; 4(4): 95-104
ISSN 2308-3840 (online)

META-ANALYSIS

Gadoxetic acid-enhanced magnetic resonance imaging for the detection of small hepatocellular carcinoma (≤ 2.0 cm) in patients with chronic liver disease: A meta-analysis

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Conflict-of-interest statement: The authors declare that there is no conflict of interest related to this study.

Data sharing statement: Supplementary files provide detailed description of 10 studies included in the meta-analysis.

Manuscript source: Unsolicited manuscript

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Received: March 11, 2016
Peer-review started: March 14, 2016
First decision: April 14, 2016
Revised: April 28, 2016
Accepted: June 14, 2016

Article in press: June 16, 2016
Published online: August 26, 2016

Abstract

AIM

To perform a meta-analysis assessing the value of gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-MRI) in detecting small hepatocellular carcinoma (HCC) (≤ 2.0 cm) in patients with chronic liver disease.

METHODS

Databases, including MEDLINE and EMBASE, were searched for relevant original articles published from January 2008 to February 2015. Data were extracted, and summary estimates of diagnostic accuracy indexes such as sensitivity, specificity, diagnostic odds ratio, predictive value, and areas under summary receiver operating characteristic curve were obtained using a random-effects model, with further exploration employing meta-regression and subgroup analyses.

RESULTS

In 10 studies evaluating 768 patients, pooled per-lesion sensitivity of Gd-EOB-DTPA was 91% (95%CI: 83%-95%), with a specificity of 95% (95%CI: 87%-98%). Overall positive likelihood ratio was 18.1 (95%CI: 6.6-49.4), for negative likelihood ratio (NLR) of 0.10 (95%CI: 0.05-0.19) and diagnostic odds ratio of 182 (95%CI: 57-581). Subgroup analysis suggested that diagnostic performance of Gd-EOB-MRI for sub-centimeter HCC (≤ 1.0 cm) detection was low, with a sensitivity of 69% (95%CI: 59%-78%). In studies with both Gd-EOB-MRI and diffusion-weighted imaging (DWI) performed, Gd-EOB-MRI/DWI combination was more sensitive than Gd-EOB-DTPA alone, whether for small lesions (86% *vs* 77%) or sub-centimeter ones (80% *vs* 56%).

CONCLUSION
A limited number of small studies suggested that Gd-EOB-MRI has good diagnostic performance in the detection of small HCC (≤ 2.0 cm) among patients with chronic liver disease, but relatively lower performance for detection of sub-centimeter HCC (≤ 1.0 cm). Combination of Gd-EOB-MRI and DWI can improve the diagnostic sensitivity of MRI.

Key words: Liver-specific agent; Gadoxetic acid-enhanced Magnetic resonance imaging; Hepatocellular carcinoma; Meta-analysis

Core tip: Although studies have shown that gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-MRI) had good diagnostic performance in detecting hepatocellular carcinoma (HCC), the results about small HCC have been limited thus far by a small number of included patients, especially for subcentimeter lesion (≤ 1.0 cm). Therefore, we performed a systematic review and meta-analysis to obtain updated diagnostic performance values of Gd-EOB-MRI for the detection of small HCC in terms of different size (≤ 2.0 cm *vs* ≤ 1.0 cm), different technique (Gd-EOB-MRI alone *vs* combined diffusion weighted imaging).

Shan Y, Gao J, Zeng MS, Lin J, Xu PJ. Gadoxetic acid-enhanced magnetic resonance imaging for the detection of small hepatocellular carcinoma (≤ 2.0 cm) in patients with chronic liver disease: A meta-analysis. *World J Meta-Anal* 2016; 4(4): 95-104 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i4/95.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i4.95

INTRODUCTION

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related deaths worldwide[1]. Despite important advances in multidisciplinary therapies, complete curative treatment of early-stage small HCC (≤ 2.0 cm, including hypervascular and hypovascular HCC) remains the only option for long-term patient survival. Studies indicated that the smaller the HCC, the less likely the occurrence of microvascular invasion[2]. The International Consensus Group for Hepatocellular Neoplasia also stated that early HCC, well differentiated HCC with a vaguely nodular appearance and less than 2 cm in size, should be considered a carcinoma *in situ*, and is characterized by an indistinct margin without capsule formation, vascular invasion or intrahepatic metastasis[3,4]. In addition, the smaller the HCC, the more likely it is for local ablation to be complete[5,6]. It is therefore important to perform early diagnosis of HCC when the tumor is still as small as possible. However, in small nodules (≤ 2.0 cm), an atypical vascular profile is not uncommon, which constitutes a challenge for definitive radiological diagnosis. These lesions may, in fact, represent either early HCCs or preneoplastic lesions, such as high-grade dysplastic nodules[3,7,8]. They are often hypovascular and lack arterial enhancement or a washout pattern[7,8]. In addition, many small, benign nodules (*e.g.,* cirrhosis-related nodules and arterioportal shunts) can mimic small HCC in patients with cirrhosis.

The hepatocyte-specific magnetic resonance imaging (MRI) contrast agent gadoxetic acid (Gd-EOB-DTPA; Bayer Healthcare, Berlin, Germany) can provide, in a single examination, comprehensive hemodynamic information during early dynamic phases and improved lesion detection in the hepatobiliary phase (HBP)[9-11]. HBP images better depict HCC, which appears as a hypointense lesion, compared with conventional dynamic gadolinium-enhanced images, on which small HCCs frequently show only arterial enhancement without early washout[12-14].

Although studies have compared gadoxetic acid-enhanced MRI (Gd-EOB-MRI) with multidetector computed tomography (MDCT) and Gd-DTPA-enhanced MRI for detecting small HCC, and shown that HBP imaging provides a slight improvement in the diagnosis of small HCC[10,11,15-22], the results were limited thus far by the small numbers of included patients, especially for sub-centimeter lesions (≤ 1.0 cm). Therefore, we performed a systematic review and meta-analysis of the literature published in the past few years, to obtain updated diagnostic performance values of Gd-EOB-MRI for detecting small HCC in patients with chronic liver disease.

MATERIALS AND METHODS

Literature search

A comprehensive literature search of studies evaluating human subjects was performed by two investigators (Yan Shan and Peng-Ju Xu) to identify articles on diagnostic performance of Gd-EOB-MRI in detecting small HCC in patients with chronic liver disease. The PubMed and EMBASE databases were searched from January 2008 to February 2015, for English articles with the following keywords: (Gd-EOB-DTPA or gadoxetic acid or gadoxetate disodium or Gd-EOB-MRI) and (hepatocellular carcinoma or liver neoplasms) and (sensitivity or specificity or false negative or false positive or diagnosis or detection or accuracy). Other databases, such as Web of Science, Scopus and the Cochrane Database of systematic review, were also searched for relevant articles. All review articles, comments, case reports, letters, and unpublished articles were eliminated. Articles found to be eligible based on title, and subsequently abstract, were then selected to determine further suitability for inclusion in this study.

Inclusion and exclusion criteria

Studies were included if, in addition, all the following inclusion criteria were met: (1) articles reported in

English; (2) Gd-EOB-MRI with HBP performed to evaluate small HCC in patients with chronic liver disease; (3) histopathology analysis and/or cross-sectional imaging follow-up used as the reference standard; (4) data based on per-lesion basis; and (5) sufficient data reported to construct 2 × 2 contingency tables. Authors of studies with insufficient published data were contacted personally in an effort to retrieve the missing data. Studies were excluded if either of the following exclusion criteria were applicable: (1) fewer than 10 patients; or (2) multiple reports published for the same study population (in this case, the publication with the most details and/or most recently published was selected).

Data extraction and quality assessment

The methodological quality of the included studies was assessed independently by the same two investigators using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool in Review Manager 5.3, which evaluates the risk of bias for four domains and clinical applicability for three domains of study characteristics. The QUADAS-2 tool was used as provided by the QUADAS-2 group[23]. Meanwhile, relevant data were also extracted from each study, including author, publication year, sample size, number of lesion, description of study population (age and gender), study design (case series, case control, cohort study, and randomized controlled trial), patient enrollment (consecutive or not), etiology of liver disease, magnetic field strength, dose of Gd-EOB-DTPA, number of experts who assessed and interpreted Gd-EOB-MRI data, and mean time interval between Gd-EOB-MRI and histopathology. Any mention Gd-EOB-MRI measurement blinding to histopathologic and clinical results and/or other diagnostic methods used was also recorded. For each study, the number of true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) findings was recorded for Gd-EOB-MRI in detecting small HCC in patients with chronic liver disease. Disagreements were resolved by discussion between the two investigators.

Statistical analysis

Diagnostic accuracy: Data regarding diagnostic performance of Gd-EOB-MRI were combined quantitatively across eligible studies. In addition, bivariate random-effects model and hierarchical summary receiver operating characteristic (ROC) were used to obtain summary estimates of sensitivity and specificity[24]. Diagnostic odds ratio (DOR) and likelihood ratios are also metrics that combine both sensitivity and specificity in calculations.

Heterogeneity exploration and subgroup analysis: Heterogeneity was assessed by likelihood χ^2 tests and I^2. The I^2 index is a measure of the percentage of total variation across studies due to heterogeneity beyond chance. Values of 30%-60%, 50%-90%, and 75%-100% may represent moderate, substantial and considerable heterogeneity, respectively[25]. In likelihood ratio χ^2 tests, $P < 0.05$ was regarded as indicative of apparent heterogeneity. The threshold effect is an important extra source of variation in meta-analysis. If there is a threshold effect, an inverse correlation appears; in this case, combining study results involving fitting a ROC curve was better than pooling sensitivities and specificities. To assess threshold effect existence, sensitivity and specificity for Gd-EOB-MRI were plotted on an ROC plane[26]. Moreover, Spearman correlation coefficient (between the logit of sensitivity and that of specificity) was determined for Gd-EOB-MRI. In case no threshold effect was found in the meta-analysis, meta-regression analysis with a backward stepwise algorithm was then performed to investigate other sources of heterogeneity for Gd-EOB-MRI. Such factors included the type of study design (case series, case control, cohort study, and randomized controlled trial), use of the same reference standard, enrollment patients, age (year), gender, sample size, number of lesions, diameter of HCC, MRI field strength, dose of Gd-EOB-DTPA, mean time interval between Gd-EOB-MRI and histopathology, reviewers (year of experience), and publication year.

Subgroup analysis was performed according to lesion size ($\leqslant$ 2.0 cm *vs* $\leqslant$ 1.0 cm); We also compared the performance of Gd-EOB-MRI alone with that of its combination with DWI by analyzing studies that used these diagnostic methods in the same patients.

Publication bias: Publication bias was assessed visually using a scatterplot of the inverse of the square root of the effective sample size ($1/ESS^{1/2}$) against diagnostic log odds ratio, which should have a symmetric funnel shape when no publication bias is present. Formal testing for publication bias was conducted using a regression of diagnostic log odds ratio against $1/ESS^{1/2}$ and weighting according to the effective sample size, with $P < 0.01$ indicating significant asymmetry[27].

Statistical analysis was performed with Stata statistical software Version 12 (StataCorp LP, Texas, United States) and Meta-DiSc statistical software, version 1.4 (Unit of Clinical Biostatistics, Ramo'n y Cajal Hospital, Madrid, Spain). $P < 0.05$ was considered statistically significant.

RESULTS

Literature search and study selection

After a comprehensive computerized search was performed, with reference lists extensively cross-checked, this research yielded 387 primary studies; 265 studies were excluded after title and abstract review. One handred twelve articles were excluded after reviewing the full article for the following reasons: (1) study aim did not reveal Gd-EOB-MRI in detecting HCC (n = 45); (2) results were obtained from a combination of HCC, hepatic metastasis and other hepatic diseases that could not be differentiated for assessment of single disease (n = 9); (3) no results regarding Gd-EOB-DTPA

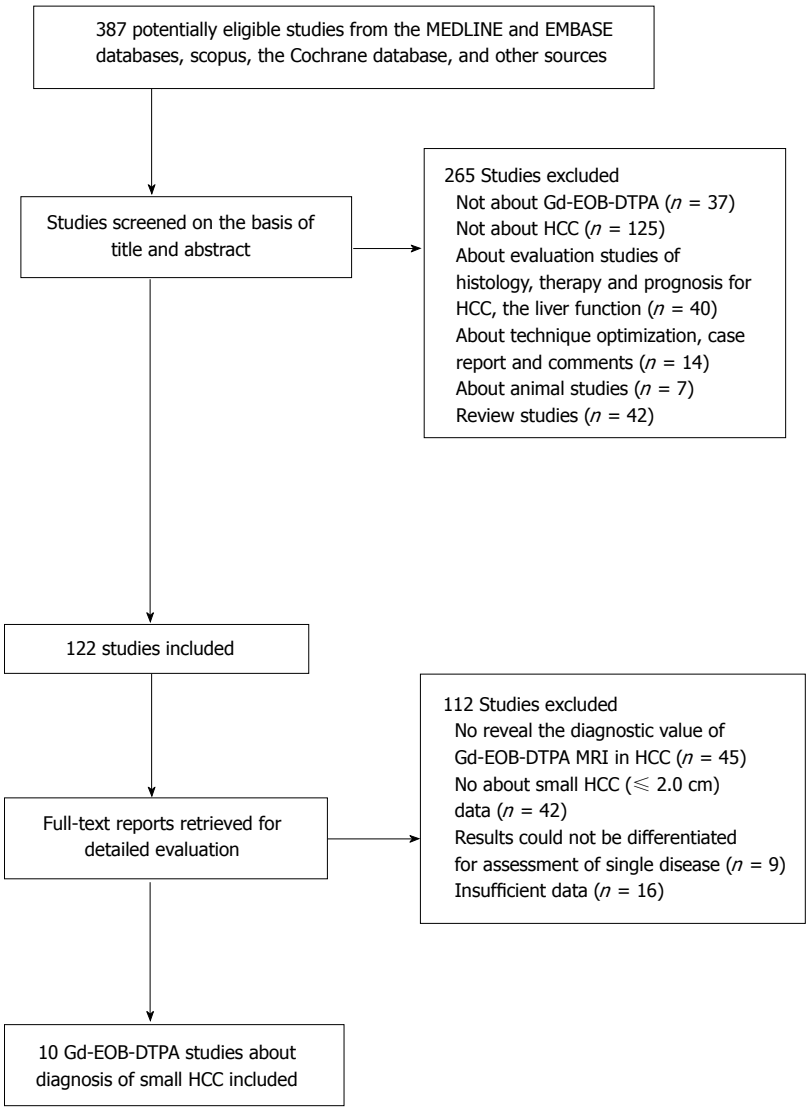

Figure 1 Flow chart for articles identified and included in this meta-analysis. HCC: Hepatocellular carcinoma.

in diagnosis of small HCC (n = 42); and (4) too little data reported to allow construction of a 2 × 2 table of TP, FN, FP and TN values (n = 16). Therefore, a total of 10 studies[9-11,17-21,28,29], which fulfilled all inclusion criteria, were considered for the analysis. The detailed procedure of study selection in the meta-analysis is shown in Figure 1.

Study description

The important characteristics of the included studies are detailed in Supplement file for review. In brief, there were no cohort or randomized controlled studies. Most studies were case series. Of all 10 studies, 7 enrolled patients retrospectively[9,11,18-21,29], while 3 stated that they were prospective[10,17,28]. All 10 studies enrolled patients in a consecutive manner[9-11,17-21,28,29]. A total of 768 patients were enrolled in the eligible studies.

There were 5 studies with MRI examinations performed with a 1.5 Tesla device[9,10,17,19,20]; 4 studies performed MRI examinations with 3.0 Tesla devices[11,18,21,29]. In the remaining study, MRI examinations were performed with 3.0 Tesla device in comparison with 1.5 Tesla device[28]. One report used a fixed dose of 10 mL of Gd-EOB-DTPA[11], while in the other 9, Gd-EOB-DTPA was administrated according to the manufacturer's instructions at 0.025 mmol per kilogram body weight. Evaluation of Gd-EOB-DTPA results was carried out in a blinded fashion in all 10 studies[9-11,17-21,28,29]. The reference standard depended solely on explanted livers in only two studies[20,21].

Assessment of study quality and publication bias

Study quality assessment data obtained with the QUADAS-2 tool are summarized in Figure 2. There were no studies considered to be at low risk of bias for all domains. The included studies being case series or of case-control design, a high risk of bias for patient selection was introduced. The substantial risk of bias regarding patient flow and timing mainly arose from that more than half of these studies used a combination of histopathologic findings and cross-section imaging follow-up as reference standards; this may result in verification bias. There was also a considerable risk of bias regarding the reference standard, as 2 studies reported that the pathologist was not blinded to imaging test results, while 4 others did not mention pathologist

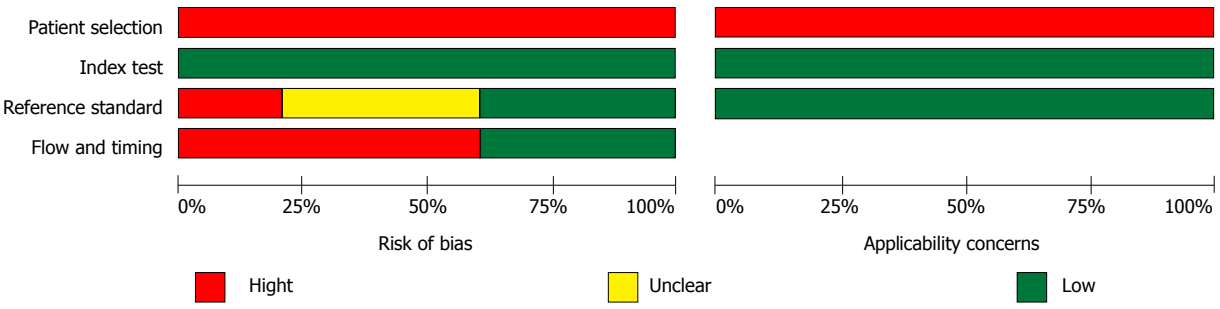

Figure 2 Grouped bar charts showing results of study quality assessment with the QUADAS-2 tool. The charts show the cumulative results of the 10 included studies in terms of risk of bias (left) and concerns regarding applicability (right) according to each QUADAS-2 domain.

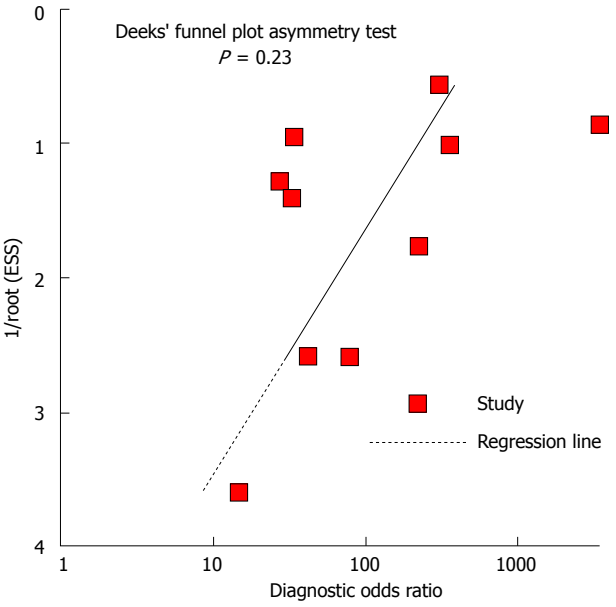

Figure 3 Results of Deeks' funnel plot asymmetry test for publication bias. The nonsignificant slope indicates that no significant bias was found. ESS: Effective sample size (P = 0.23).

blinding to index test results.

A nonsignificant slope was obtained for Deeks' funnel plot asymmetry tests (Figure 3), indicating that no significant bias was found (P = 0.23).

Diagnostic performance of Gd-EOB-MRI in detecting small HCC

Overall small HCC (≤ 2.0 cm): When studies used multiple readers, giving a range of accuracy, we selected the average result for analysis. Pooled sensitivity of Gd-EOB-MRI was 0.91 (95%CI: 0.83-0.95), for a specificity of 0.95 (95%CI: 0.87-0.98). DOR was 182 (95%CI: 57-581). The detailed sensitivity and specificity data, with 95%CIs for each individual study are provided as a Forest plot in Figure 4. Likelihood ratio syntheses yielded an overall positive likelihood ratio (PLR) of 18.1 (95%CI: 6.6-49.4) and negative likelihood ratio (NLR) of 0.10 (95%CI: 0.05-0.19). The scattergram of PLR and NLR is shown in Figure 5.

Hierarchical summary receiver operator characteristic (HSROC) curves (Figure 6) showed good diagnostic performance for Gd-EOB-MRI for all the studies combined. The area under the curve of the HSROC was 0.97 (95%CI: 0.96-0.99).

Subgroup analysis

There were three studies with reported results concerning Gd-EOB-MRI for diagnostic performance of sub-centimeter HCC (≤ 1.0 cm)[17,18,21]. For the sub-centimeter HCC subgroup, pooled sensitivity and specificity were 0.69 (95%CI: 0.59-0.78) and 0.94 (95%CI: 0.88-0.98), respectively. Sensitivity for sub-centimeter lesions (0.69) was relatively low than values obtained for all small HCCs (0.91).

Comparison against Gd-EOB-MRI combined with DWI

Gd-EOB-MRI used alone and in combination with DWI were compared for performance by analyzing 3 studies that employed these diagnostic methods for the same patients[18,21,29]. The results suggested that Gd-EOB-MRI combined DWI was more sensitive compared with Gd-EOB-MRI alone, whether for small HCC or sub-centimeter lesions (Table 1).

Heterogeneity and meta-regression analysis

The heterogeneity of sensitivity and specificity tests was highly significant (P < 0.05 and I^2 > 75%) (Figure 4). This was strong evidence of between-study heterogeneity. Sensitivity and specificity for Gd-EOB-MRI were plotted on an ROC plane, and no curvilinear pattern was found. In addition, Spearman correlation coefficient (between the logit of sensitivity and that of specificity) for Gd-EOB-MRI was 0.237, with a P value of 0.51. No threshold effect was found in this meta-analysis. Meta-regression analysis showed that study design contributed significantly to heterogeneity (P = 0.04). However, other factors did not significantly contribute to study heterogeneity (P > 0.05).

DISCUSSION

Our results confirmed that Gd-EOB-MRI accurately detects small HCC. Previous reports showed that most HCCs appear as relatively low signal intensity lesions in HBP imaging because of inexistent gadoxetic acid uptake. Therefore, gadoxetic acid is expected to

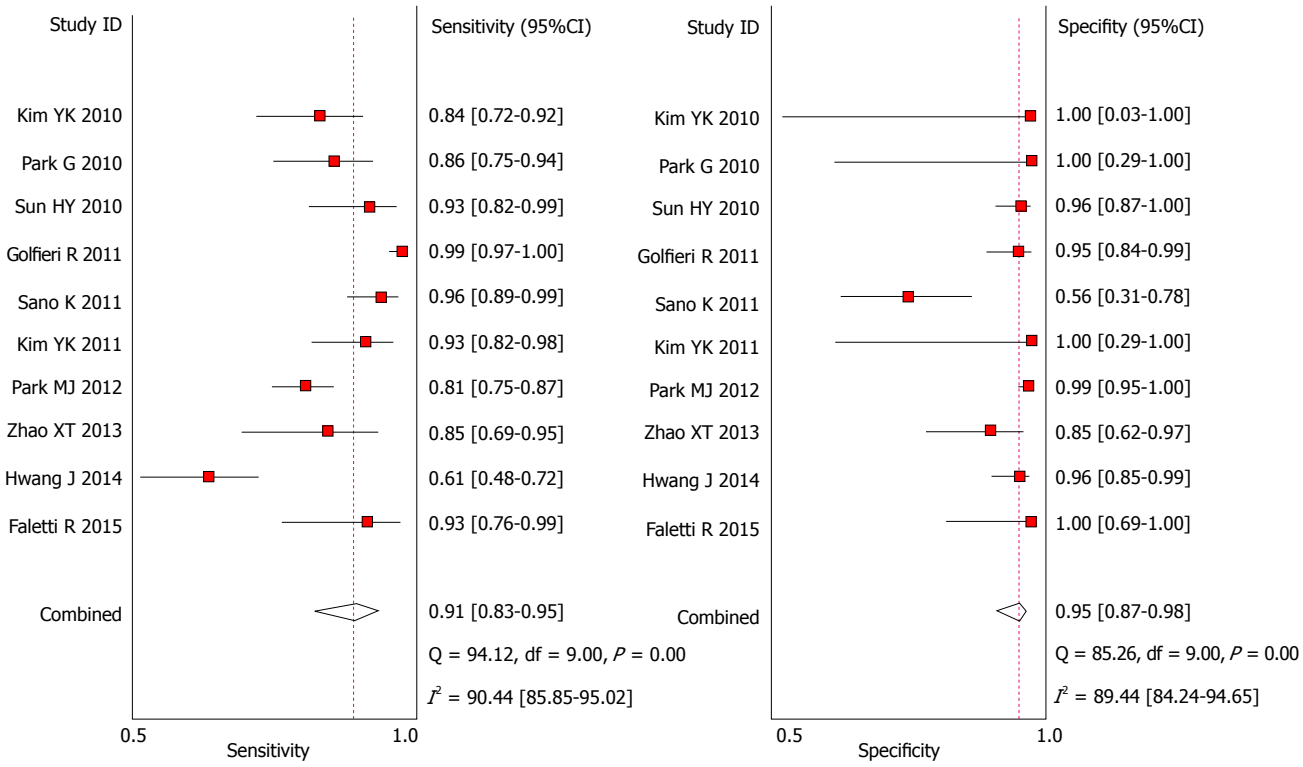

Figure 4 Forest plot of pooled sensitivity and specificity of gadoxetic acid-enhanced magnetic resonance imaging in detecting small hepatocellular carcinoma among patients with chronic liver disease. Summary sensitivity and specificity were 0.91 (95%CI: 0.83-0.95) and 0.95 (95%CI: 0.87-0.98), respectively.

Table 1 Comparison of the diagnostic performance of Gadoxetic acid-enhanced magnetic resonance imaging alone and combined with diffusion weighted imaging[1]

Diagnostic methods compared	Lesion size	Ref.	Summary sensitivity, % (95%CI)	Summary specificity, % (95%CI)
Gd-EOB-DTPA MRI alone	≤ 2.0 cm	[18,21,28]	0.77 (0.71-0.82)	0.97 (0.93-0.99)
Combined Gd-EOB-DTPA MRI with DWI			0.86 (0.82-0.90)	0.92 (0.88-0.96)
P value			0.0047	0.975
Gd-EOB-DTPA MRI alone	≤ 1.0 cm	[18,21]	0.56 (0.45-0.69)	0.96 (0.90-0.99)
Combined Gd-EOB-DTPA MRI with DWI			0.80 (0.68-0.88)	0.94 (0.87-0.98)
P value			0.0013	0.709

[1]The diagnostic performance of each modality was compared by using the *Z* test for Summary sensitivity and specificity, $P < 0.05$ was considered indicative of a statistically significant difference. Gd-EOB-MRI: Gadoxetic acid-enhanced MRI; DWI: Diffusion-weighted imaging.

enable excellent lesion detection and characterization for both hypervascular and hypovascular HCCs by arterial phase and HBP imaging, respectively[11,14,16,17,30]. Several studies suggested that hypointensity in HBP imaging, even in the absence of arterial phase hyperenhancement, is highly predictive of pre-malignant or malignant lesions[7,9,20]. Furthermore, early HCC is essentially hypovascular, with no dominant arterial blood supply. It is not surprising that conventional arterial phase imaging techniques are inefficient in evaluating early HCCs, with Gd-EOB-MRI HBP imaging being the only technique that successfully depicts early HCCs[19]. Previous findings confirmed that arterial hypervascularization delineation in HCC by gadoxetic acid is comparable to that by conventional Gd-DTPA[9]. Furthermore, sensitivity for hypervascular HCC detection is sufficiently high, and HBP images provide an added value to sensitivity, when Gd-EOB-MRI is applied[9,17,19]. However, previous studies found that HBP imaging is almost the only technique that successfully depicts hypovascular HCCs[17,19]. Dynamic contrast-enhanced MRI reveals hypervascular HCCs based on altered arterial vascularity due to the development of unpaired arteries and sinusoidal capillarisation[31]. A pathological explanation of arterial enhancement absence is the weak development of nontriadal arteries in hypovascular nodules (including early HCC), which make their characterization based on dynamic MR phases impossible[3,4,32]. However, hypovascular nodules usually show organic anion-transporting polypeptide under-expression, which begins prior to changes in hemodynamics. Therefore, they appear hypointense in HBP images[33].

We hypothesized that Gd-EOB-MRI and DWI combination has superior diagnostic performance over Gd-EOB-MRI alone, as it provides multi-parametric data

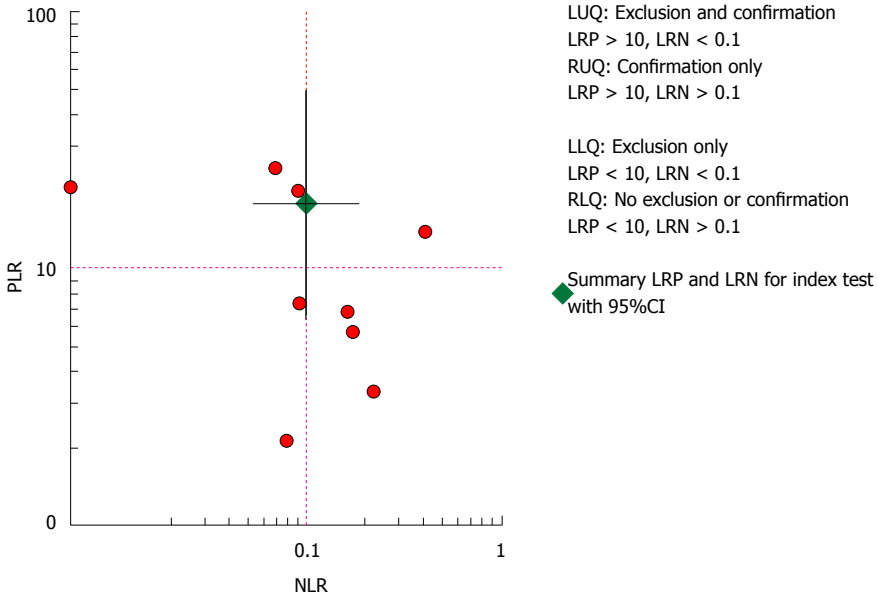

Figure 5 Scattergram of positive likelihood ratio and negative likelihood ratio. Pooled estimates for gadoxetic acid-enhanced MRI in the detection of small HCC were: PLR of 18.1 (95%CI: 6.6-49.4) and NLR of 0.10 (95%CI: 0.05-0.19). PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

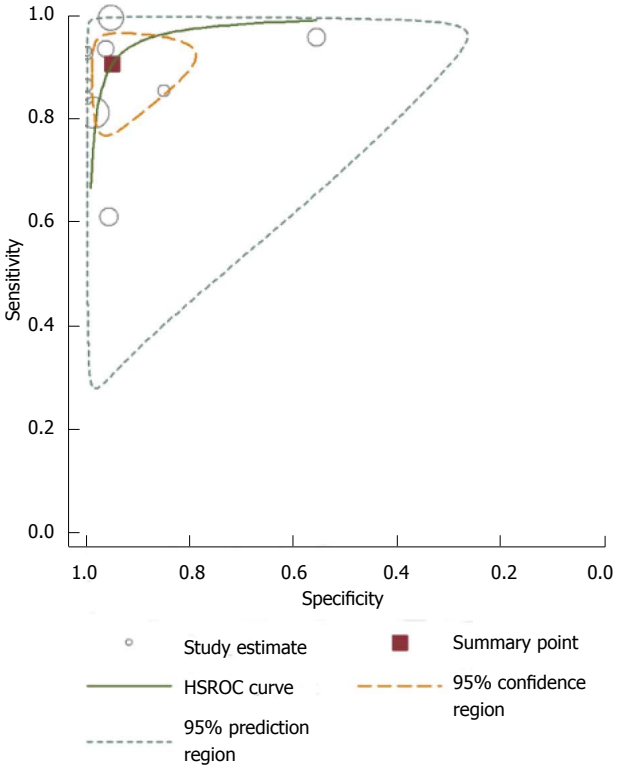

Figure 6 Hierarchical summary receiver operating characteristic plot of per-lesion diagnostic accuracy for gadoxetic acid-enhanced magnetic resonance imaging detection of small hepatocellular carcinoma in patients with chronic liver disease for the 10 included studies. The 95% confidence region and 95% prediction region around the pooled estimates illustrate the precision with which the pooled values were estimated (confidence ellipse of a mean) and to show the extent of between-study variation (prediction ellipse; likely range of values for a new study). HSROC: Hierarchical summary receiver operator characteristic.

such as vascular changes, hepatocyte function and cellular density[20,21,34]. In addition, given the importance of HBP imaging in the detection of small hypovascular HCCs, a considerable number of small HCCs are easily overlooked in the HBP set, particularly the lesions located adjacent to vessels. Thus, hyperintensity on DWI could contribute to improving the detection of small HCCs by helping reduce the number of mischaracterized lesions and allowing more accurate characterization of equivocal lesions[16,18,20,21].

With regard to tumor size in HCC, confident diagnosis of HCC in sub-centimeter hepatic nodules has been considered unfeasible[14,35]. Although per-lesion sensitivity estimates for MR imaging in sub-centimeter HCCs may be further increased with Gd-EOB-DTPA use, it is still relatively low[18,21]. The results of this meta-analysis showed the relatively low per-lesion sensitivity estimates for sub-centimeter HCCs. One possible explanation is that HBP ability to detect malignancies might be reduced in decompensated cirrhosis because gadoxetic acid uptake and metabolism are related to hepatocyte function. Previous studies showed a trend toward decreased sensitivity of Gd-EOB-MRI for detecting small HCC with increasing cirrhosis severity[21,36]. It is clear that a cirrhotic liver shows restricted diffusion in line with hepatic fibrosis severity[37]. Thus, it remains difficult to identify HCC in severely cirrhotic liver in any imaging studies; this limits the usefulness of both Gd-EOB-MRI and DWI in patients with decompensated liver cirrhosis[18,20,21,36], especially for sub-centimeter HCCs.

Investigation of reasons for heterogeneity rather than computation of a single summary measure is an important purpose of meta-analysis[38]. Significant heterogeneity was found in pooled analysis of the included 10 studies. Spearman correlation analysis demonstrated there was no significant threshold effect. This work suggested that study design may affect diagnostic accuracy. These findings corroborated a recently published report[39], which showed that case series studies have significantly higher per-lesion sensitivity than case-control studies. Therefore, it is important that

future studies adopt study designs that better control biases and provide higher levels of evidence such as cohort studies and randomized controlled trials.

In seven previous meta-analyses[40-46], investigators evaluated the detection of HCC of any size by Gd-EOB-DTPA, three of which yielded a subgroup analysis for small HCCs[40-42]. In a recent meta-analysis, Kierans *et al*[47] evaluated the diagnostic performance of dynamic contrast-enhanced MRI for the detection of small HCC with subgroup analysis of Gd-EOB-MRI, whose results were consistent with our findings[40-42,47]. However, compared with the above reports, this study has the following characteristics: All cases in the included literatures had a history of chronic liver disease; subgroup analysis for the diagnostic performance of Gd-EOB-MRI and DWI combination in the detection of sub-centimeter HCC was performed. In addition, in two recent meta-analyses[39,48], investigators compared the diagnostic performance of ultrasonography, CT and MRI in the detection of HCC of any size without subgroup analysis. Therefore, in comparison with the above previous meta-analyses, we expanded the evaluation to combined Gd-EOB-MRI and DWI, and detectability for sub-centimeter HCC.

Our meta-analysis has several limitations. First, data were collected in a prospective manner, with a limited number of studies (only three studies), which resulted in a major methodologic limitation of including many studies with retrospective patient data collection. Pooling such suboptimal retrospective results may have caused a bias toward increased diagnostic sensitivity[49]. Second, participants in included studies were both patients diagnosed with HCC based on findings prior imaging tests or other clinical data and those suspected of having HCC, which might have caused selection bias. In addition, limited numbers of lesions were diagnosed during liver transplantation (only two studies), which might have resulted in an overestimation of the diagnostic performance of Gd-EOB-MRI by decreasing the number of false-negative lesions. Finally, considerable heterogeneity was observed with per-lesion analysis. For example, whether or not interpretation of pathology data was blinded from Gd-EOB-MRI seemed to be a common weakness, and only 4 studies used the same reference standard. Furthermore, we found substantial variation in the way Gd-EOB-MRI findings were used for the identification of HCC, indicating a lack of consensus regarding diagnostic criteria and thresholds. To overcome the heterogeneity of the present data, we used both the hierarchical summary ROC model and the random-effects model. Because the 95%CIs were not substantially wide, we believe that the present results are valuable. However, heterogeneity in this type of diagnostic study remains a point of concern.

In conclusion, our meta-analysis showed that Gd-EOB-MRI has good diagnostic performance in the detection of small HCC (≤ 2.0 cm) among patients with chronic liver disease, but relatively lower performance for the detection of sub-centimeter HCC (≤ 1.0 cm). Combination of Gd-EOB-MRI and DWI can improve the diagnostic sensitivity of MRI for the detection of small HCC.

COMMENTS

Background

In recent years, gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-MRI) has shown that hepatobiliary phase imaging provides improvement in the diagnosis of small hepatocellular carcinoma (HCC ≤ 2.0 cm). However, the results are limited thus far by small numbers of included patients with chronic liver disease, especially for sub-centimeter lesions (≤ 1.0 cm). In addition, no consensus is available regarding diagnostic performance of combined Gd-EOB-MRI and diffusion weighted imaging (DWI) in the detection of small HCC.

Research frontiers

Despite important advances in multidisciplinary therapies, complete curative treatment of early-stage small HCC remains the only option for long-term patient survival. Thus, the importance of early detection of HCC has been emphasized, especially with the application of noninvasive multi-modality imaging.

Innovations and breakthroughs

In this study, the authors investigated the value of Gd-EOB-MRI for the diagnosis of sub-centimeter HCC. It is also believed to be the first meta-analysis evaluating combined Gd-EOB-MRI and DWI in the detection of small HCC.

Applications

This meta-analysis showed that Gd-EOB-MRI has relatively lower performance for the detection of sub-centimeter HCC, and combination of Gd-EOB-MRI and DWI can improve diagnostic sensitivity. In clinical practice, the addition of DWI to routine protocol of Gd-EOB-MRI may help increase sensitivity in the detection of small HCC, especially for sub-centimeter lesion.

Peer-review

This is a meta-analysis evaluating Gd-EOB-MRI for the detection of small HCC in patients with chronic liver disease, showing that Gd-EOB-MRI has good diagnostic performance for the detection of small HCC; in addition, Gd-EOB-MRI and DWI combination improves the diagnostic sensitivity of MRI for detecting small HCC. The methods used in this study are state of the art, and data are well presented and discussed in the light of the current literature.

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