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Efficacy and safety of imiquimod for verruca planae: A systematic review

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Abstract

Objective: To assess the efficacy and safety of imiquimod for treating verruca planae.

Methods: We searched the Pubmed, Cochrane Register of Controlled Trials, EMbase, CBM, CNKI and Wanfang databases (Chinese) to collect randomized controlled trials (RCTs). We screened the retrieved studies according to the predefined inclusion and exclusion criteria, evaluated the quality of include studies, and performed meta-analyses using the Cochrane Collaboration's RevMan 5.1. Software.

Results: Twenty-six RCTs involving 2169 patients with verruca planae were included and assessed. At the end of the 6th and ≥8th week, the effective rate of topical imiquimod was obviously higher than that of control [RR=1.42, 95%CI (1.27, 1.60), P <0.00001; RR=1.43, 95%CI (1.22,1.67), P<0.00001]. The effective rate of imiquimod cream was higher than tretinoin cream, tazarotene gel and other antiviral drugs. [RR=1.41, 95%CI (1.25, 1.59), P <0.00001; RR=1.76, 95%CI (1.48, 2.10), P<0.00001; RR=1.71, 95%CI (1.29, 2.26), P =0.0002]. However, the effectiverate of imiquimod cream was lower than 5-ALA-PDT (RR=0.6, 95%CI (0.5, 0.71), P<0.00001).

Conclusions: The limited evidence demonstrates that topical imiquimod is safe and efficient. More multiple central RCTs with large samples are required to verify these conclusions.

Introduction

Verruca planae are warts caused by the human papilloma virus (HPV), mostly by HPV type3, 10, 28 and 41. They primarily affect children and young adults [1]. The treatment cycle is usually prolonged. Current treatment options are anti-viral, immune-modulation and destruction of the infected tissue.

Imiquimod is a low molecular weight, synthetic immune response modifier which does not exert its antiviral effects directly on virus-infected cells. Imiquimod induces the production of antiviral cytokines that enhance cellular immunity necessary for the control or elimination of HPV infection. Imiquimod is often prescribed for condyloma acuminatum [2]. In recent years, there are reports that it has been used for flat warts and molluscum contagiosum, with satisfactory curative effect [3]. Here we performed a systematic review on the efficacy and safety of imiquimod cream in the treatment of verruca planae in order to provide the evidence for clinical decision.

Materials and methods

Eligibility criteria

Inclusion and exclusion criteria were determined before the search was conducted. We included studies comparing the efficacy and safety of Imiquimod with other drugs on patients with verruca planae. Included studies must be randomized controlled trial (RCT). Case reports, reviews and document of incomplete data were excluded.

Intervention measure

The test group for 5% imiquimod cream alone or in combination with other treatment methods.

Outcome indicator

Cured: skin lesions completely disappeared or decreased >90%. Significantly improved: skin lesions decreased >60% (or >70%); Improved: over 30%, but less than 70% of decrease of skin lesions; Invalid: less than 30% in decrease of kin lesions. The effective rate is the sum of cured and significantly improved by the total number of the tested patients.

Data sources and searches

To identify relevant studies, three reviewers (Z.X.R, X.B.H, H.X.J) systematically searched MEDLINE, Cochrane Central Register of Controlled Trials, Embase, China National Knowledge Infrastructure database (CNKI), China Biology Medicine disc (CBM) and Wanfang Data Knowledge Service Platform. Search terms were based on specific agents ("Imiquimod," "Verruca Planae," "Plane Warts," "Flat Warts,"

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"Systematic review," "Randomized controlled trial," "Treatment").

Study selection

To determine eligibility for inclusion in the review, we searched all titles and abstracts that analyses the efficacy of imiquimod for treating verruca planae with control group. There were no limitations on the study design, participant's age, gender, or nationality. We identified 68 articles in the initial search. Two of them were in English, others in Chinese. Through manual review of the citations from these articles, we removed 39 articles including general reviews, case reports, investigative research, commentaries and other non-clinical trials. We identified 28 original studies that were eligible for inclusion criteria assessment. After reviewing the full text of these 28 studies, we excluded 2 articles of non RCT nature. In the end, we selected 26 studies that met the inclusion criteria for this systematic review [4-29]. The search processes are presented in chart in Figure 1.

Data extraction

Studies were selected independently by two researchers who used the same criteria. The third researcher was involved in the discussion if there were controversial issues. If the information is not complete or not clear, we contact original author to obtain the information and determine whether the study will be included.

Quality assessment

We used RevMan 5.1 (Review Manager Version 5.1) to analyze the quality of the data, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (Figure 2).

Data synthesis and analysis

We analysed the data using RevMan 5.1.Chi square test was used to test for heterogeneity. The degree of heterogeneity between studies was assessed using the I^2 test. And I^2 value >50% was considered there existed substantial heterogeneity. In such a case, random effects model was used. Results were expressed with relative risk (RR) and 95% confidence interval (CI) and the test level α=0.05. Publication bias was displayed graphically by using funnel plots (Figures 1 and 2).

Result

Characteristics of the included publications

The basic characteristics of the included studies were shown in Table 1, including the total number of cases, the number of excluded and the lost, the age, course of disease, the number of effective cases and the intervention measures.

Quality assessment

All included studies were referred to the randomized grouping, and only 4 studies [4,9,10,20] described the details. All the studies were unclear in reporting allocation concealment and blinding. 5 studies [5,7,8,14,29] reported the number of withdraw. Assessment of methodological quality of included studies was presented in Figure 2.

Therapeutic evaluation

Total effect: Twenty six RCTs involving 2169 patients with verruca planae were included and assessed. Results showed that the effective rate of topical imiquimod combined with intramuscular injection or other oral drugs in the treatment of flat wart was obviously higher than using other drugs alone. (RR=1.35 (95% CI 1.181.54.), P<0.00001) (Figure 3), 10 studies [4,10-11,17-18,20-21,23,27,29] described the efficacy at the end of 4 weeks. As there exist statistical heterogeneity among the studies (P<0.00001, I^2=82%), meta-analysis was performed using a random effects model. The results showed that the efficacy of test group was significantly higher than that in control group. The difference had no statistical significance. (RR=1.81, 95%CI (0.91, 1.54), P=0.21) (Figure 4A.2.1.1.). 6 studies [5,17-18,20-22] described the efficacy at the end

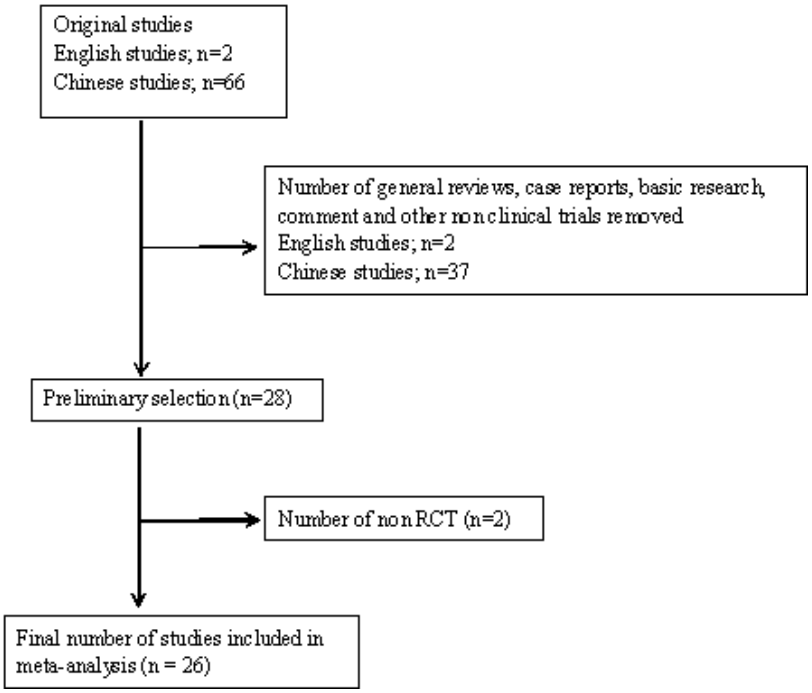


Figure 1. Flowchart of literature search and study selection.

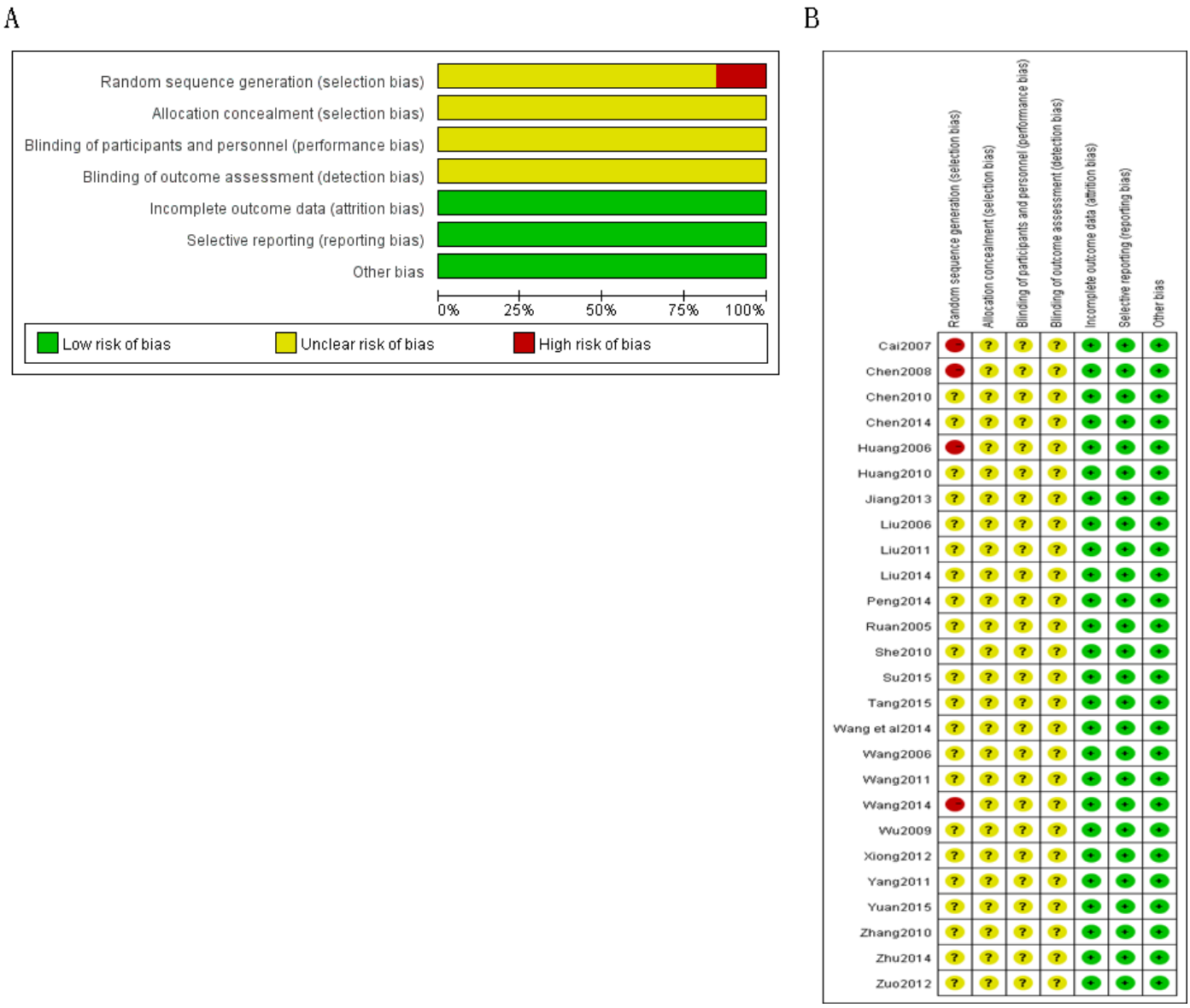


Figure 2. Assessment of methodological quality of included studies (**2A.**Risk of bias graph; **2B.** Risk of bias summary).

of 6 weeks. As there was no statistical heterogeneity (P=0.08, I^2=48%), meta-analysis was performed using a fixed effects model. The results showed that the efficacy in the test group was significantly higher than that in control group (RR=1.42, 95%CI (1.27, 1.60), P<0.00001) (Figure 4B), 19 studies [4,6-21,24-26,28] described the efficacy at the end of 8 weeks. As there existed statistical heterogeneity (P<0.00001, I^2=80%), meta-analysis was performed using a random effects model. The results showed that the efficacy in the test group was significantly higher than that in control group (RR=1.43, 95%CI (1.22, 1.67), P<0.00001] (Figure 4A.2.1.2.).

Imiquimod cream *vs.* Tretinoin cream: A total of 8 studies [4-11] were included, of which 3 studies [4-6] of the test group is imiquimod cream combined with BCG -PSN, the control group is tretinoin cream combined with BCG-PSN, 3 studies [7-9] of the test group was imiquimod cream only, the control group was tretinoin cream only. The 2 studies [10,11] of test group was imiquimod cream combined with tretinoin cream once a day each, the control group was only tretinoin cream once per day; results showed that the effective rate in imiquimod group was significantly higher than tretinoin cream group (RR=1.41, 95%CI (1.25, 1.59), P<0.00001); the effective rate of imiquimod combined with BCG-PSN group was higher than that of tretinoin cream combined with BCG-PSN group (RR=1.56, 95%CI (1.27, 1.91), P<0.0001); the effective rate of imiquimod alone or in combination with tretinoin cream group was higher than that of tretinoin cream alone group (RR=1.32, 95%CI (1.14, 1.54), P =0.0003) (Figure 5A.3.1.1.).

Imiquimod cream *vs.* Tazarotene gel: A total of 4 studies [12-15] were included, of which the test group was imiquimod cream combined with tazarotene gel once a day each, the control group was tazarotene gel alone once per day. The results showed the effective rate in test group was higher than tazarotene group (RR=1.76, 95%CI (1.48, 2.10), P<0.00001) (Figure 5A.3.1.2.). One study [16] reported that the effective rate in imiquimod group was higher than that of adapalene group.

Table 1. Characteristics of included studies.

First author; publication year	Age (year)		Course of disease		Exit number	Total number	Effective	course of treatment	Intervention measures	
	T	C	T	C	(T/C)	(T/C)	(T/C)		T	C
Wang (2014)	19-39	20-40	3m-2y	2m-2y	-	40/40	1m:17/15	1m, 2m, 3m	5% imiquimod cream, 1 time per day, external use and BCG-PSN, 3 times per week, 2 ml each time, intramuscular injection	0.1% vitamin A acid cream, 1 time per day and BCG-PSN, 3 times per week, 2 ml each time, intramuscular injection
							2m:30/18			
							3m:34/21			
Liu (2014)	12-34		7m-3.5y		3	37/37	24/14	6w	5% imiquimod cream, 1 time per day, external use and BCG-PSN, every other day, intramuscular injection	0.1% vitamin A acid cream, 1 time per day, external use and BCG-PSN, every other day, intramuscular injection
Huang (2010)	8-40		1w-2y		-	40/38	34/21	8w	5% imiquimod cream, 1 time per day, external use and BCG-PSN, 3 times per week, 2 ml each time, intramuscular injection	0.1% vitamin A acid cream, 1 time per day, external use and BCG-PSN, 3 times per week, 2 ml each time, intramuscular injection
Ruan (2005)	10-45		1m-51m		4	34/33	26/18	8w	5% imiquimod cream and 0.025% vitamin A acid cream, every other day, alternative external use	0.025% vitamin A acid cream, 1 time per day, external use
Zuo (2012)	10-43		1m-5y		5	35/33	29/17	8w	5% imiquimod cream and 0.025% vitamin A acid cream, every other day, alternative external use	0.025% vitamin A acid cream, 1 time per day, external use
Chen (2008)	6-41		3w-4y		-	23/22	13/10	8w	5% imiquimod cream, every other day, external use	0.1% vitamin A acid cream, 1 time per day, external use
Huang (2006)	12-51		2w-2.5y		-	32/26	4w:25/16	8w	5% imiquimod cream, every other day, external use	0.05% vitamin A acid cream, 1 time per day, external use
							8w:26/16			
Wang (2006)	15-46		2w-2y		-	60/58	45/32	4w	5% imiquimod cream, every other day, external use	0.1% vitamin A acid cream, 1 time per day, external use
Chen (2014)	15-34	14-35	half month-36m 1m-36m		-	45/37	32/16	8w	5% imiquimod cream and tazarotene gel, every other day, alternative external use	0.1% tazarotene gel, 1 time per day, external use
Xiong (2012)	10-42		6w-3y		-	46/48	42/25	8w	imiquimod cream and tazarotene gel, every other day, alternative external use	tazarotene gel, 1 time per day, external use
Yang (2011)	29.9		6m-15y		3	34/31	26/17	8w	5% imiquimod cream and tazarotene gel, every other day, alternative external use	0.05% tazarotene gel, 1 time per day, external use
Zhang (2010)	12-45		1m-6y		-	47/81	33/24	8w	imiquimod cream and tazarotene gel, every other day, alternative external use	tazarotene gel, 1 time per day, external use

Yuan (2015)	13-51		2m-4y		-	52/42	41/23	16w	5% imiquimod cream and adapalene gel every other day, alternative external use	adapalene gel, 1 time per day, external use
Peng (2014)	12-42	15-45	1m-2y	15d-3m		110/120	2w:66/55	2w, 4w, 6w	5% imiquimod cream and adapalene gel, 1 time per day, external use	adapalene gel, 1 time per day, external use
							4w:77/51			
							6w:97/80			
Chen (2010)	11-42		9m-6y		-	59/57	2w:9/5	2w, 4w, 6w, 8w	5% imiquimod cream, 1 time per day, external use and BCG-PSN, every other day, 1ml each time, intramuscular injection	matrix, every other day, external use and BCG-PSN, every other day, 1ml each time, intramuscular injection
							4w39/25			
							6w:51/37			
							8w:56/42			
She (2010)	18-47		1m-4y		-	34/34	18/14	8w	5% imiquimod cream, 1 time per day, external use and famciclovir tablets, 2 times per day, 0.2 g, oral administration	famciclovir tablets, 2 times per day, 0.2g, oral administration
Cai (2007)	7-40		half of month-24m		-	32/31	2w:2/2	2w, 4w, 6w, 8w	5% imiquimod cream, every other day, external use	placebo, every other day, external use
							4w:4/2			
							6w:6/2			
							8w:10/3			
Wang (2011)	17-38	18-40	2m-3y	3m-4y	-	45/40	2w:6/3	2w, 4w, 6w, 8w	5% imiquimod cream, 1 time per day, external use and transfer factor, 3mg, twice per week, subcutaneous injection	transfer factor, 3mg, twice per week, subcutaneous injection
							4w:16/9			
							6w:25/12			
							8w:35/16			
Zhu (2014)	-		3m-8y		-	30/30	23/10	6w	5% imiquimod cream, 1 time per day, external use and placenta polypeptide injection, 1 time per day, intramuscular injection	placenta polypeptide injection, 1 time per day, intramuscular injection
Liu (2011)	8-42		20d-2y		-	40/39	40/26	4w	5% imiquimod cream, every other day, external use and IFN-a2b cream, 3 times per day, external use	IFN-a2b cream, 3 times per day, external use
Tang (2015)	14-51	16-50	-		-	41/40	41/37	8w	imiquimod cream, every other day, external use and ALA-PDT, 1 time per 7 to10 days	ALA-PDT, 1 time per 7 to10 days
Liu (2006)	13-36	13-40	4m-3y	3m-4y	-	45/45	29/15	8w	5% imiquimod cream, every other day, external use	Ftibamzone liniment, 2 times per day, external use

Wu (2009)	12-50		2w-6y		-	35/32	30/18	8w	5% imiquimod cream, 1 time per day, external use and Pidotimod powder, two copies per day, oral administration	Penciclovir cream, 1 time per day, external use and Pidotimod powder, two copies per day, oral administration
Wang (2014)	18-26	19-25	1y-3y	1y-3y	-	35/35	20/35	4w	5% imiquimod cream, every other day, external use	ALA-PDT, once a week
Su (2015)			-		-	38/40	22/40	8w	5% imiquimod cream, every other day, external use	ALA-PDT, 1 time per 10 to 14 days
Jiang (2013)	18-26	19-25	1y-3y	1y-3y	1	15/16	10/16	3w	5% imiquimod cream, every other day, external use	ALA-PDT, once a week

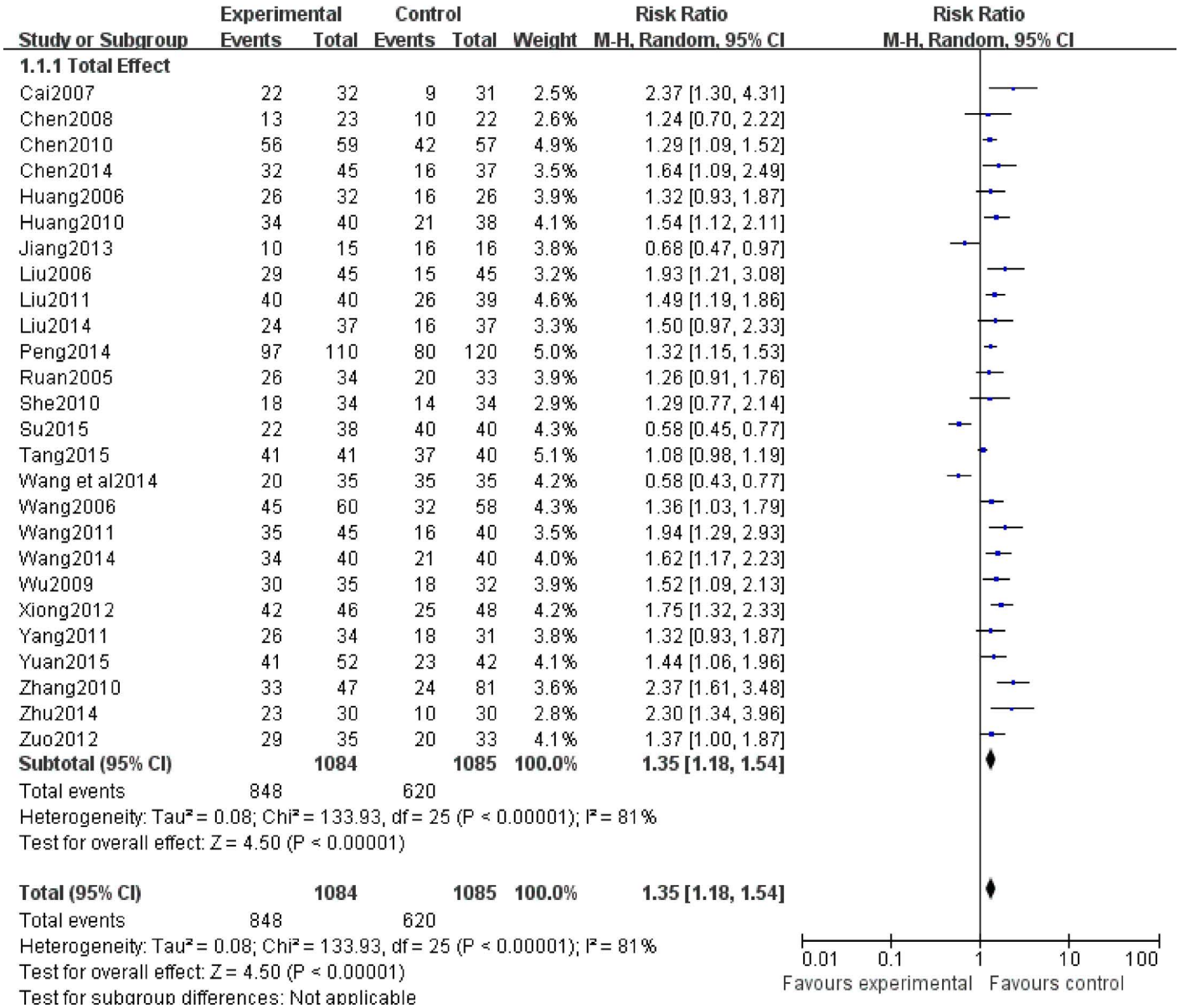
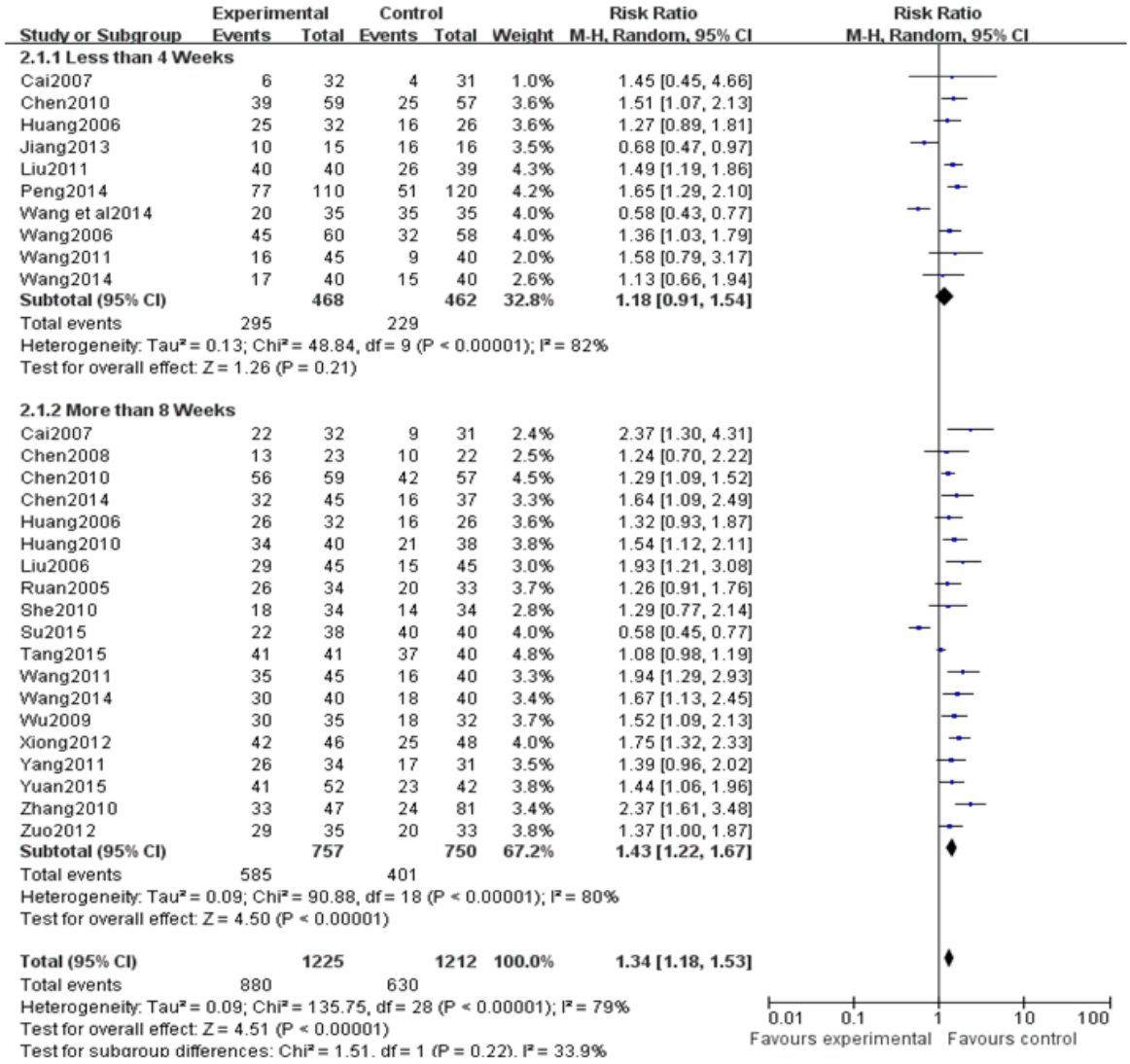


Figure 3. Forest plot for the total effect of imiquimod in the treatment of verruca planae.

A



B

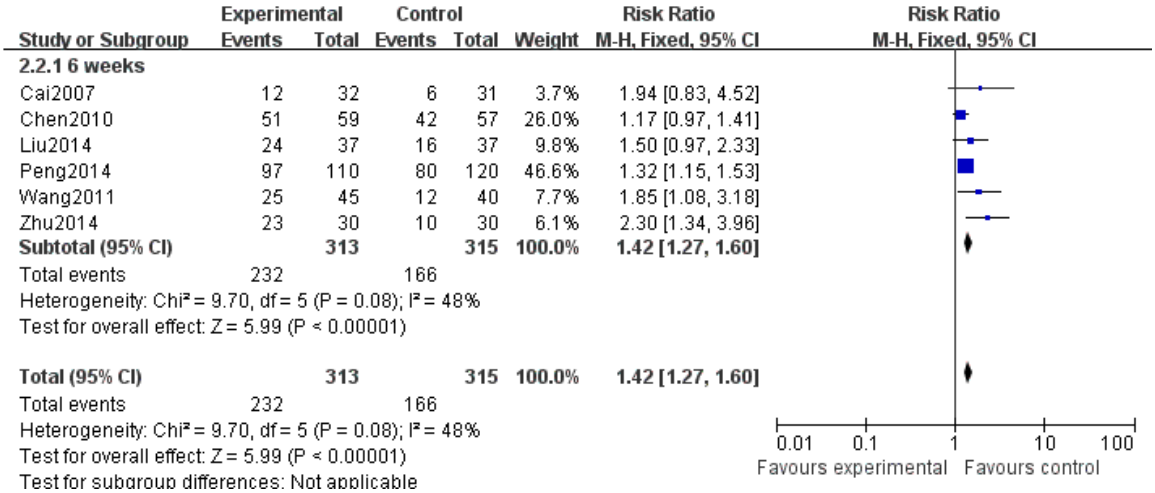
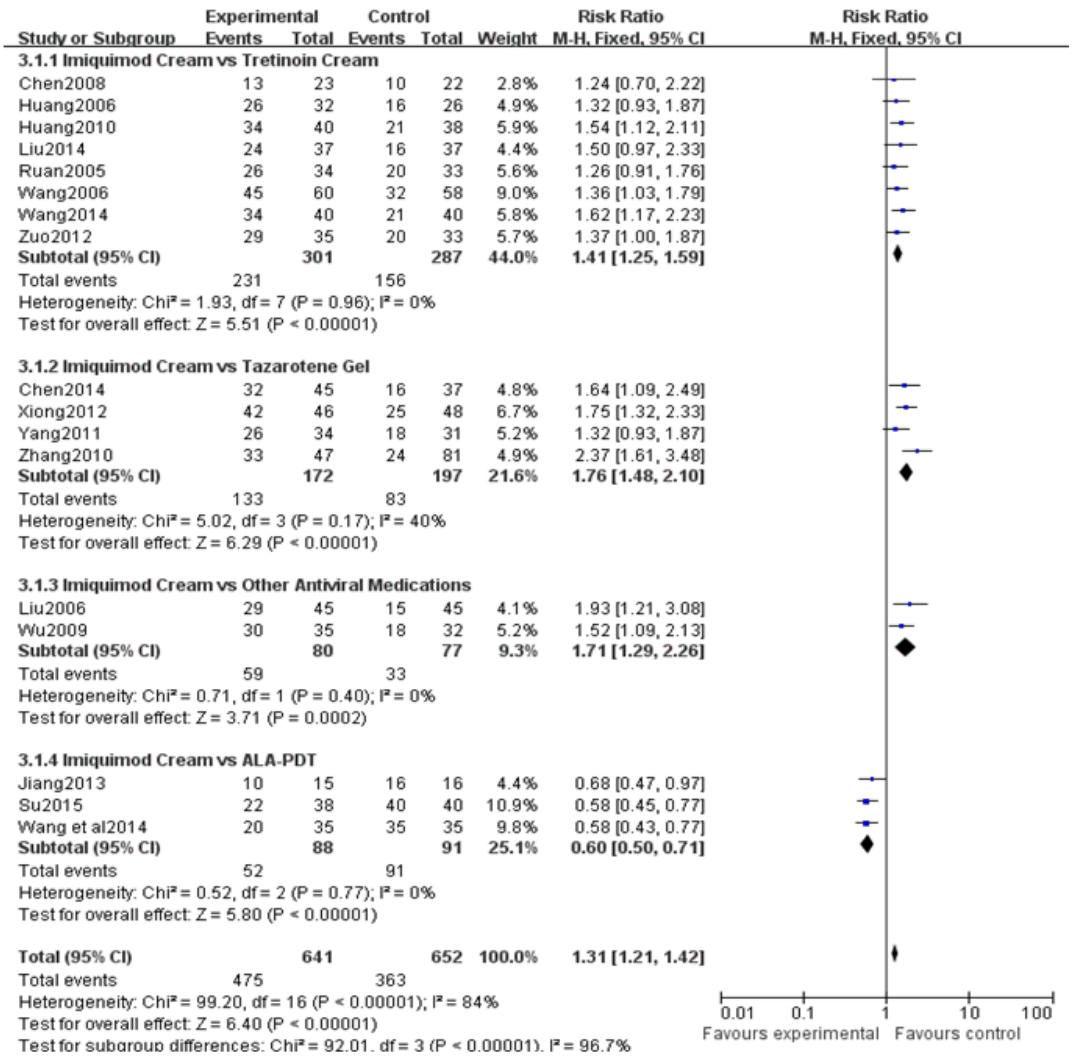


Figure 4. Forest plot for treatment course (**4A. 2.1.1.** Efficacy in less than 4 weeks; **4A. 2.1.2.** Efficacy in more than 8 weeks; **4B.** Efficacy in 6 weeks).

A



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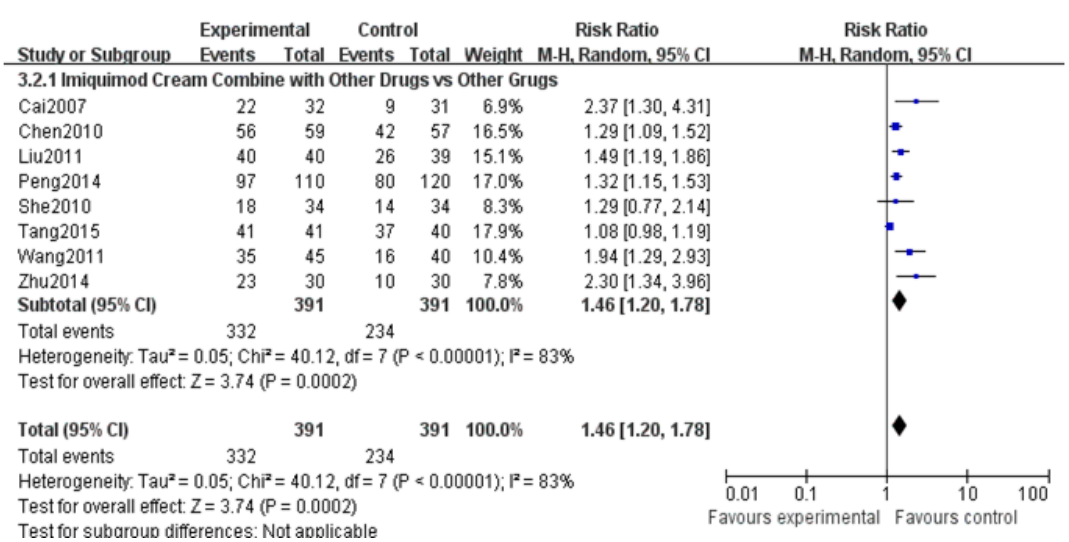

Figure 5. Forest plot for Intervention measures (**5A. 3.1.1.** Forest plot for comparison ofimiquimod cream therapy with tretinoin cream therapy; **5A. 3.1.2.** Forest plot for comparison of imiquimod cream therapy with tazarotene gel therapy; **5A. 3.1.3.** Forest plot for comparison of imiquimod cream therapy with other antiviral medications; **5A. 3.1.4.** Forest plot for comparison of imiquimod cream therapy with ALA-PDT therapy; **5B.** Forest plot for comparison of imiquimod cream combine with other drugs therapy with other drugs)

Imiquimod Cream *vs.* Other antiviral medications: A total of 2 studies [25,26] were included, of which the test group was imiquimod cream alone or combined with pidotimod powder. Pidotimod powder alone served as control group. The results showed that the effective ratein imiquimod group was higher than in control group (RR=1.71, 95%CI (1.29, 2.26), P=0.0002) (Figure 5A.3.1.3.).

Imiquimod Cream *vs.* ALA-PDT: A total of 3 studies [27-29] were included, of which of the test group was imiquimod cream alone once every other day and ALA-PDT in the control group. The results showed that the effective rate of imiquimod group was lower than that of ALA-PDT group (RR=0.6, 95%CI (0.5, 0.71), P<0.00001) (Figure 5A.3.1.4.).

Imiquimod Cream Combined with Other Drugs *vs.* Others drugs: A total of 9 studies [16-24] were included, of which the test group was imiquimod cream alone or in combination with adapalene, BCG-PSN, famciclovir, transfer factor, Alpha 2 b interferon cream , ALA-PDT and placebo. And adapalene, BCG-PSN, famciclovir, transfer factor, Alpha 2b interferon cream and ALA-PDT were in the control groups, correspondingly. Results show that the effective rate of imiquimod (or in combination with other drugs) was higher than that of the control groups (RR=1.46, 95% CI (1.20, 1.78), P=0.0002) (Figure 5B). The heterogeneity is significant due to the different intervention measures for each of the control groups.

Adverse events: 22 studies [4-17,21,23-29] reported the adverse events. However, the adverse reactions were mild, and patients could recover soon after stopping or reducing the drugs.

Publication bias

Funnel plot analysis showed that the figure was basically symmetrical upside down funnel, and there was no significant publication bias (Figure 6).

Follow up

8 studies reported the follow-up. Lium [5] followed the patients for 2 months. There was no recurrence in the cured patients in the test group, and 2 cases who significantly improved also cured. Some of the patients in the control group had increase in the lesions. Huangm [6] followed the patients for a month, test group had 2 recurrent cases, control group had 7 recurrent cases. Tang [24] closely observed the cured patients in both groups for 3 months. The recurrence cases in the test group in 1, 2, 3 months were less than those in the control group, the difference was statistically significant (P<0.05), Wang [4] followed up for 3 months then observed both groups showed no recurrence. Su [28] followed up the cured patients for 3 months; there were no cases of recurrence. Jiang [29] followed up for half a year, the test group and the control group had no recurrence. Liu [25] followed up for 2 months the results showed no recurrence, Wu [26] followed up for six months, 2 recurrent cases occurred in the treatment group (5.71%) and 4 in the control group (12.5%).

Discussion

During the search, we found that many articles reported that imiquimod cream alone or in combination with other drugs could make a good effect on treatment of verruca planae. But there was no systematic review about efficacy and safety of imiquimod cream on the verruca planae. This systematic review included all RCT on verruca planae. The meta-analysis results showed that the effective rate of imiquimod cream in the treatment of flat wart was higher than other treatments. We found that the effective rate of ALA-PDT in treatment of verruca planae was more effective than imiquimod. However, the report about ALA-PDT use was limited.

The review made the conclusion that imiquimod was efficacy and safe on verruca planae based on the limited evidence. First, owing to the studies of imiquimod on verruca planae was investigated mostly

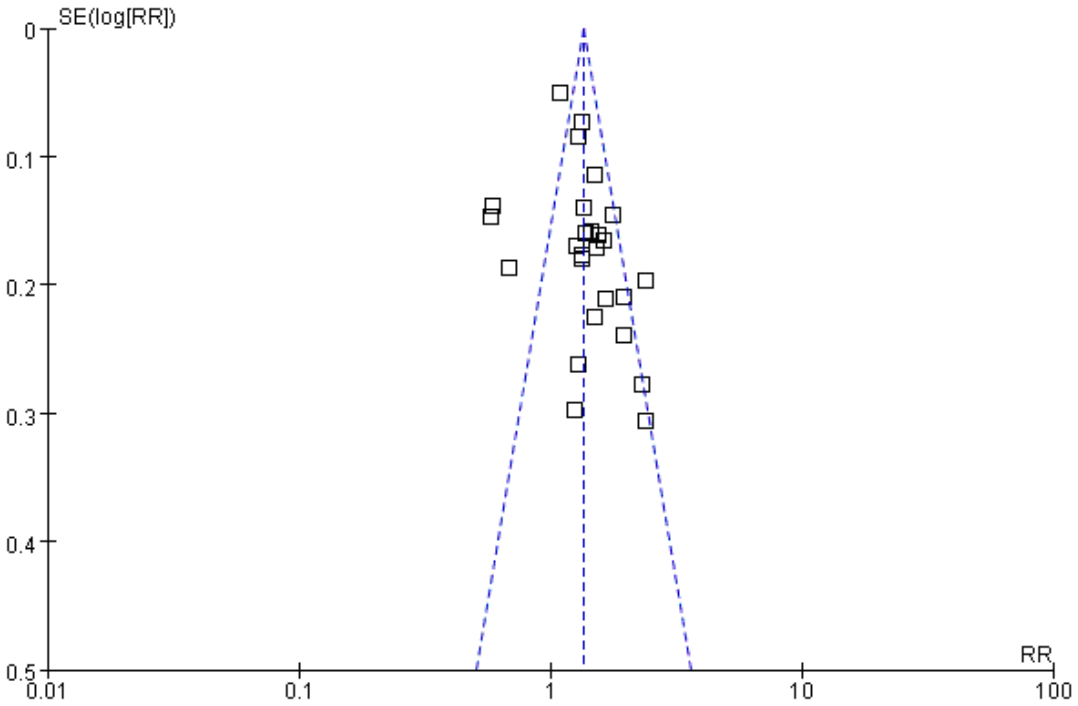

Figure 6. Funnel plot for evaluating publication bias.

by Chinese, we included a total of 26 randomized controlled trials that all come from China which may cause language bias. Second, quality of the included studies was not high, only 1 study described exclusion or losses of follow up. All studies did not mention the blinding and allocation concealment which may cause selection bias, performance bias and measurement bias. Third, the intervention measures in the test group and the control group were different, and it was difficult to extract and combine the data. Fourth, each of the intervention measures included in the studies was relatively small. Therefore, the results of these articles need to be confirmed and re-evaluated by more RCTs with high quality, large scale and multicenteral.

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