Intralesional Measles, Mumps, and Rubella Vaccine for Cutaneous Warts: A Systematic Review and Meta-analysis

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ABSTRACT

Background. Warts, caused by the human papilloma virus (HPV), are mucocutaneous proliferations controlled by cell-mediated immunity. Intralesional immunotherapy with measles, mumps, and rubella (MMR) vaccine, is postulated to induce a higher immune response for clearance of lesions.

Objective. To assess the efficacy, safety and effect on recurrence of intralesional MMR vaccine for the treatment of warts.

Methods. We searched online databases for randomized controlled trials on intralesional MMR vaccine for warts. Effects measured were the complete clearance of target and distant warts, adverse events noted and recurrence after treatment duration.

Results. Four RCTs comparing intralesional MMR vaccine and placebo were assessed. Meta-analysis showed a risk ratio of 0.24 [95% CI: 0.18, 0.34] favoring intralesional MMR vaccine and a highly significant difference in completely clearing target warts (P-value <0.00001) versus placebo. Three of the 4 trials assessed response of distant warts showing a risk ratio of 0.28 [95% CI: 0.08, 0.96] and a significant difference (P=0.04) versus placebo. Pain and flu-like symptoms were the most common side effects with no recurrence seen after 3-6 months.

Conclusions. Intralesional MMR vaccine significantly reduces and clears target and distant warts as compared to placebo. It is a generally safe intervention with lasting effect assessed up to 6 months follow-up.

Key Words: Warts, Verruca, Intralesional, MMR

INTRODUCTION

Cutaneous warts are common cutaneous and mucosal infection of children and adults. *Common warts* or *verruca vulgaris* is a proliferation of infected keratinocytes caused by the human papilloma virus (HPV).[1] The infections caused by HPV do not produce other signs and symptoms whether local or systemic but induces a slow, concentrated accumulation of keratinocytes. The lesions produced by infection of the virus may enlarge into masses which are persistent and recalcitrant.[2] They commonly present as hyperkeratotic, exophytic papilloma or plaques with punctate black dots commonly associated with HPV types 1, 2, 27, and 57. These are commonly found on the fingers but can occur anywhere on the skin. *Plantar and palmar warts* are thick endophytic papules. Patients with plantar warts usually complain of pain from pressure when walking. *Flat warts* are flat-topped, relatively smooth skin-colored to brown papules usually on the hands, arms or face. HPV 3 or 10 usually causes this

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type. *Condyloma acuminata*, also termed anogenital warts, are usually found on mucosal surfaces such as the anal area and external genitalia and usually present as exophytic papillomas. Different types of the virus cause the spectrum of lesions found on the body with some having oncogenic potential.[3]

Measles, mumps, and rubella vaccine is injected subcutaneously at 12 months of age for 2 doses, given 4 weeks apart.[4] Some studies that tested effects of intralesional MMR vaccine have postulated that higher response may be attributed to the vaccine having three synergistic antigens which could potentiate a higher response by the immune system.[5]

It is suggested that wart proliferation is controlled by cell-mediated immunity as it was observed that there is uncontrolled proliferation of warts in immunocompromised patients (HIV, transplant patients, etc.). Supporting this finding is the significant influx of CD4+ lymphocytes in lesions which spontaneously resolve.[6] Human Papilloma Virus infection activates the body's immune response, which includes production of antibodies and activation of Th1 lymphocytes. Interleukin-4 which helps in antibody secretion and IL-12, a pro-inflammatory cytokine seen in a Th1-mediated immune response, are also seen.[7] Another mechanism postulated is that there is proliferation of blood mononuclear cells, which leads to a Th1 cytokine response thereby activating cytotoxic T cells and natural killer cells.

Intralesional immunotherapy employs the ability of the body's immune system to recognize antigens to mount a Th1-mediated delayed-type hypersensitivity response. This in turn increases the ability of the body to recognize and fight the virus to achieve complete clearance of lesions and lasting resolution. Furthermore, destruction of other lesions on the body, aside from the treated lesion, can also be achieved due to the stimulated immune response. It is associated with the release of IL-2, IL-4, IL-5, IL-8, TNF-alpha and IFN-gamma.[6]

There have already been studies that dealt with intralesional immunotherapy for warts. Previous studies have been done using tuberculin, BCG, mumps, candida and trichophyton, and measles/mumps/rubella vaccines. All these were proven efficacious in reducing the size and clearing of verruca.[6,8,9,10]

Verruca is a very common condition affecting all ages. Many modalities have been utilized in the management of warts. Methods include electrodessication, cryotherapy, use of keratolytics such as salicylic acid, trichloroacetic acid and lactic acid and surgical excision. Oral medications such as zinc supplementation, levamisole and cimetidine as well as other immunotherapeutic agents like imiquimod, interferons and contact sensitizers are also being used.[6] Although several options are available for treatment, there is still no method that has been proven to achieve complete clearance of lesions. The abovementioned modalities are also oftentimes painful, traumatic and costly. This study aimed to review the existing evidence on the efficacy of intralesional immunotherapy of MMR vaccine in cutaneous warts.

OBJECTIVES

Primary objectives

- To assess the efficacy of intralesional measles, mumps and rubella (MMR) vaccine for the treatment of cutaneous warts
- To assess the efficacy of intralesional MMR vaccine for the treatment of distant warts

Secondary objectives

- To assess the safety of intralesional MMR vaccine for the treatment of cutaneous warts
- To assess the recurrence of lesions after treatment

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) comparing intralesional immunotherapy using measles, mumps, and rubella vaccine to placebo and other forms of immunotherapy were included. No exclusions were made with regard to language and sample size.

Types of participants

All patients who were clinically diagnosed with cutaneous warts were included. No exclusions were made based on the age or sex of participants, duration of the condition, type of cutaneous warts involved and number of lesions.

Types of interventions

Included studies for this analysis were controlled trials that compared intralesional measles, mumps and rubella vaccine versus other types of intralesional immunotherapy and intralesional placebo. No exclusions were made based on the duration of treatment.

Types of outcome measures

1. **Primary outcomes** – refers to clinical cure at the end of intervention.
   a. Clinical cure refers to complete clearance of target warts and of distant warts

2. **Secondary outcomes**
   a. Adverse events – any new symptoms experienced during the administration of intervention and during treatment
   b. Recurrence rate – the proportion of patients with appearance of new lesions on the designated follow-up period after achieving clinical cure or improvement

Search methods for identification of studies

Electronic searches

We searched PubMed and The Cochrane library using keywords namely, "warts", "verruca", "intralesional MMR", "MMR". Search was filtered to clinical trials.

Searching other resources

Ongoing systematic reviews on the topic were checked on PROSPERO (International Prospective Register of Systematic Reviews). We also searched HERDIN, the Trip Database, Journal of the American Academy of Dermatology (JAAD) and Google scholar for articles using the abovementioned keywords.

Data collection and analysis

Selection of studies

Studies were selected by consensus of three independent review authors. Initial screening of articles were done through scanning of the titles and abstracts for inclusion to the study. Duplicate articles were identified. Studies selected were controlled trials and those that measured complete clearance of lesions. Full-text articles were retrieved if inclusion criteria were unclear or could not be identified by preliminary review.

Data extraction and management

Data extracted from the included studies were design/type of trial, participant demographics (e.g. age, gender), intervention details (dose, frequency, comparator/control, duration and follow-up) and the assessed outcomes. Data on dropouts and funding sources were also noted. Two review authors using the appraisal form independently did appraisal of each journal.

Assessment of risk of bias in included studies

Validity of the included trials were independently assessed by two review authors using the Cochrane risk of bias tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8, section 8.5). Risk of bias was assessed based on these domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Included trials were categorized as low risk, unclear risk or high risk. "High methodological quality" was assigned to a study designated with low-risk in all domains; "moderate methodological quality" if one of the domains is reported as having "unclear risk"; and "low methodological quality" if any of the domains is "high risk." Any discrepancies, such as bias from company-sponsored trials and significance of dropouts, were settled by discussion between the authors, and resolved by a third assessor.

Measures of treatment effect

Treatment effect was measured using risk ratio, relative risk and absolute risk reduction with 95% confidence intervals. Data synthesis was done using the software package Review Manager 5.3 (RevMan 2014).

Unit of analysis issues

No differences were seen in the included studies regarding unit of analysis.

Dealing with missing data

Authors were contacted for further details on missing data. With no response, only available data were used in the analyses.

Assessment of heterogeneity

Heterogeneity was assessed through analysis of forest plots and by determining I^2 statistic produced by the RevMan software and was interpreted using the Cochrane Handbook for Systemic Reviews of Interventions (Chapter 9, section 9.5)

Assessment of reporting biases

Authors were contacted for missing or unclear data in the included studies. Both fixed and random-effects were determined and compared for the studies displaying heterogeneity.

Data synthesis

Studies were compared using the PICOM (Population, Intervention, Comparison, Outcome, Methods) format and summary tables were done to facilitate concise presentation of study details.

Statistical analysis was done using the Review Manager software (version 5.3). Risk ratio, relative and absolute risk reduction were computed with 95% confidence interval. Data of trials not included in the meta-analysis were discussed separately.

Subgroup analysis, investigation of heterogeneity, sensitivity analysis

A subgroup analysis was done comparing MMR vaccine versus placebo and another on the effect of the intervention on distant warts. Heterogeneity was visually assessed using the forest plot and objectively determined using the I^2 statistic. For trials with high heterogeneity, possible reasons for such were explored.

Summary of findings table

A summary of findings table was made using the GRADEpro software. Outcomes used in the meta-analysis were included. The GRADE approach to assessing quality of evidence was used.

RESULT

Description of studies

Results of the search

A total of 8 articles through the electronic searches from PubMed (n=6) and Cochrane Database (n=2) were obtained. No local trials were identified from HERDIN. Using the clinical trial filter, 3 studies were identified. Trials were also searched in Google scholar, which yielded 20 results. We identified 6 duplicates. The rest of the studies were evaluated by the titles. We retrieved 6 records for further assessment of abstracts. We excluded 3 studies as they were of a different study design (before and after studies). In total, 5 controlled trials fulfilled the inclusion criteria.

Included studies

The 5 studies, which fulfilled the inclusion criteria, are summarized in Table 1.

Design

All studies were randomized controlled trials assessing the efficacy of intralesional measles, mumps, and rubella vaccine in the treatment of cutaneous warts. (Zamanian 2014, Mohamad 2013, Nofal 2010, Shaheen 2015). They compared intralesional MMR vaccine therapy with placebo (normal saline), with the Shaheen 2015 study having an additional comparator/intervention group treated with intralesional Purified Protein Derivative (PPD). The Saini 2016 study compared intralesional MMR vaccine to paring + 100% trichloroacetic acid application.

Setting

The Mohamad 2013 (outpatient dermatology clinic of Alexandria Main University Hospital), Nofal 2010 and Shaheen 2015 (dermatology and venereology outpatient clinic of a university hospital) studies were all conducted in Egypt, while the Zamanian 2010 was conducted in Hazrat-e-Rasoul Hospital of Tehran University of Medical Sciences in Iran. The Saini 2016 was conducted in the SMGS Hospital, Government Medical College, Jammu, India.

Sample size

Sample size ranged from 30 (Shaheen 2015) to 150 (Saini 2016). A total of 436 subjects were randomized.

Participants

The total number of participants for all trials was 436. Age of participants ranged from 7 to 60 years of age. There were 221 males and 215 females. There was no difference in the baseline characteristics of the participants in the intervention and control groups across all trials. All patients were diagnosed with cutaneous warts clinically with no restrictions on the size, type and number of warts and the duration of the condition. Relevant inclusion criteria included: no concurrent systemic or topical treatment for warts; not pregnant or breastfeeding; and no other infections or febrile diseases.

Intervention

1. Treatment group: Intralesional measles, mumps, and rubella vaccine Injection

Intralesional MMR vaccine was injected to target warts in all of the four studies included. The Nofal 2010 and Shaheen 2015 based the amount of vaccine to be injected on the intradermal MMR vaccine injection reaction initially done to the study participant. The Nofal 2010 study injected MMR vaccine on the target warts at 2-week intervals until complete clearance of lesions or up to a maximum of 5 sessions. The Shaheen 2015 study gave the treatment at 3-week intervals until complete clearance at a maximum of 3 weeks. The Mohamad 2013 study injected a dose of

Table 1. Characteristics of included studies

	Zamanian, 2014	Mohamad 2013	Nofal 2010	Shaheen 2015	Saini 2016
Population	46 patients diagnosed with cutaneous warts	100 patients ages 17-36 diagnosed with plantar warts	110 patients ages 14-57 diagnosed with common warts	30 patients ages 8-38 diagnosed with cutaneous warts	150 patients diagnosed with common warts
Intervention	MMR vaccine 0.5mL	MMR vaccine 0.3mL	MMR vaccine (dose depends on intradermal MMR injection reaction)	MMR vaccine (dose depends on intradermal MMR injection reaction)	MMR vaccine 0.3 mL
Number of doses administered	Every 2 weeks x 3 injections	3 doses at 3 week intervals	Every 2 weeks until complete clearance or for a maximum of 5 sessions	Every 3 weeks until complete clearance or for a maximum of 3 sessions	Every 2 weeks for 3 treatments
Comparator	Normal saline 0.5mL	Normal saline 0.3mL	Normal saline 0.3mL	Normal saline Intralesional PPD	Paring + 100% TCA
Outcomes	Complete response of target lesions, adverse outcomes, recurrence	Complete response of target lesions and distant warts, adverse outcomes, recurrence	Complete response of target lesions and distant warts, adverse outcomes, recurrence	Complete response of target lesions and distant warts, adverse outcomes, recurrence	Reduction in size of target lesions and distant lesions
Methods	Double-blind Randomized Controlled Trial	Randomized Controlled Trial	Randomized Controlled Trial	Randomized Controlled Trial	Open label, randomized, comparative study

0.3 cc of the MMR vaccine for 3 doses at 3-week intervals. The Zamanian 2014 studied injected 0.5mL of MMR vaccine every 2 weeks for a total of 3 injections. The Saini 2016 injected 0.3 mL of MMR vaccine at 2-week intervals for 3 sessions. The lesion injected was a single target wart, usually the largest of all the warts present if there were multiple ones, in four studies. The Zamanian 2014 study injected the intervention in every single wart.

2. Control group: intralesional saline/placebo, intralesional immunotherapy (PPD)/TCA 100%

Four trials used normal saline as a comparator; however, the Shaheen 2015 study, aside from having normal saline as a comparator, had another group that used intralesional PPD as its intervention. The other study, Saini 2016, compared intralesional MMR vaccine to paring of the warts with subsequent application of 100% TCA.

Outcome detection

All studies measured the response of the target wart based on the percent decrease in size. The studies rated the outcome as complete if there is disappearance of the wart and appearance of normal skin, partial/relative if there is a reduction in size of 50-99% and no response if the reduction in size is 0-49% in the study period. Three studies measured the response in distant warts using the same grading. The Saini 2016 study graded response to treatment as grade 0 for no response or aggravation, grade I if there is <25% reduction in size, grade II if there is 26-50% reduction, grade III for 51-75% reduction and grade IV if there is >75% reduction in size. Adverse events were probed by the investigators or reported by the patients on their follow-ups. Recurrence was also assessed by the studies. Follow-up period of the Nofal 2010, Mohamad 2013 and Zamanian 2014 studies were until 6 months post-treatment whereas the Shaheen 2015 and Saini 2016 studies had their post-treatment follow-up for 3 months.

Outcomes reported

Primary Outcomes:

Table 2 shows the summary of primary outcomes for the five included studies. The review used dichotomous outcomes (complete clearance versus partial clearance + no therapeutic response).

Clinical cure:

Target warts

Clinical cure is achieved once there is disappearance of target lesions. In the 3 studies Nofal 2010, Mohamad 2013 and Shaheen 2015 there was disappearance of distant warts.

For the Nofal 2010 study, complete clinical response was seen in 57/70 (81.4%) patients in the MMR group versus 11/40 (27.5%) in the control group with a computed P-value <0.001 which showed statistical significance. The Mohamad 2013 study results showed complete response in 41/50 (82%) patients versus placebo wherein no subject showed complete cure of lesions during the treatment period. Calculated P-value was at <0.001, which again showed a statistically significant difference between intralesional MMR versus placebo. Eighteen out of 24 (75%) patients in the MMR group achieved complete clearance in the study by Zamanian 2014 versus 6/22 (27.3%) in the placebo group (P-value <0.001). Shaheen 2015 compared intralesional MMR versus intralesional PPD versus placebo. Complete clearance was achieved in 6 out of 10 (60%) participants in the PPD treatment group, 8 out of 10 (80%) in the MMR group and none in the control group. The p-value of PPD versus MMR was computed at >0.05 which showed no statistical significance between the two interventions. However, p-value of MMR versus control and PPD versus control were both at <0.001 showing a statistical significance. The Saini 2016 study compared intralesional MMR vaccine to paring and application of 100% TCA. Complete clearance of target warts was achieved in 23 out of 87 patients in the MMR group while only 5 out of 63 patients achieved complete clearance in the TCA group. The calculated p-value showed a highly statistically significant difference between the two groups (p<0.001).

Distant warts

Clearance of distant lesions was assessed by 4 studies. Nofal 2010 reported a complete clearance of distant warts in 17 out of 20 (85%) participants versus three (3) out of nine (9) (33%) in the control group. Twenty-two out of the 25 (86.9%) participants in the MMR group had complete clearance of lesions in the Mohamad 2013 study. This was in contrast to no clearance on distant lesions in the control group. The calculated p-value was at <0.001, which showed a statistically significant difference between

Table 2. Primary outcomes of included studies with intralesional MMR vaccine as intervention

		Shaheen 2015			Mohamad 2013		Nofal 2010		Zamanian 2014		Saini 2016	
		MMR (n=10)	Placebo (n=10)	PPD) (n=10	MMR (n=50)	Placebo (n=50)	MMR (n=70)	Placebo (n=40)	MMR (n=24)	Placebo (n=22)	MMR (n=87)	Placebo (n=63)
Treatment of target warts	Complete resolution	8	0		41	0	57	11	18	6	23	5
	Partial + No response	2	10		9	50	13	29	6	16	64	58
		Shaheen 2015			Mohamad 2013		Nofal 2010		Saini 2016			
		MMR (n=10)	Placebo (n=10)	PPD (n=10)	MMR (n=24)	MMR (n=24)	MMR (n=20)	Placebo (n=9)	MMR (n=24)		100% TCA + paring (n=8)	
Treatment of distant warts	Complete resolution	4	0	6	0	0	17	3	0		0	
	Partial + No response	6	10	4	24	24	3	6	24		8	

the 2 interventions. Four out of 10 patients in the MMR group had clearance of distant lesions versus none in the placebo group. However, the PPD group had a complete clearance rate of 60% (6/10) in the distant warts. There was a significant difference (P-value <0.001) between both PPD versus placebo and MMR versus placebo but no significant difference (P-value >0.05) between MMR and PPD. For the Saini 2016 study, no significant difference was seen on distant warts. There was only partial response in 6 of the 20 patients with distant warts in the MMR group while no response on distant warts was seen in the TCA group.

Secondary outcomes:

Adverse events: All studied reported on adverse events experienced during the trial. Pain during injection of the intervention was the most reported side effect in all studies. Nofal et al. reported that 85.7% of patients experienced pain during injection. One hundred percent of study participants in the Zamanian 2014 and Shaheen 2015 studies reported pain at the time of injection. The second most notable adverse event reported was flu-like symptoms. Six patients out of the 70 (8.6%) enrolled in the MMR group of the Nofal 2010 study experienced such, two patients in the Mohamad 2013 study, 30% of patients in the MMR group of the Zamanian 2014 study and 1 patient in the MMR group of the Saini 2016 study. Other side effects reported were erythema and swelling. Vasovagal attack occurred in 10% of patients in the MMR vaccine-treated group of Shaheen 2015 study with no mention of the manifestation and severity of symptoms.

Recurrence rate: A follow-up period for detection of recurrence was designated by all studies. Three studies had their follow-up periods for a duration of 6 months. Follow-up was made every two months for six months for the Nofal 2010 and Zamanian 2014 studies and every month for six months for the Mohamad 2013 study. The Shaheen 2015 study conducted a follow-up period of three months with an interval of every three weeks. The Saini 2016 study had monthly follow-ups for 3 months. No recurrence of lesions of the patients treated with intralesional MMR vaccine was reported in the follow-up periods of each study.

Risk of bias in included studies

Selection Bias

The studies by Nofal 2010, Shaheen 2015, Saini 2016 and Zamanian 2014 were assessed to have low risk of bias. The study by Mohamad 2013 was assessed as having unclear risk as there was no statement on how randomization was achieved. All of the included studies had unclear risk of bias for allocation concealment because it was not stated if the process was done for each study.

Performance Bias and Detection Bias

Only the study by Zamanian 2014 was assessed to have a low risk of performance bias. They explicitly stated in the title and methodology that the study is a double-blinded trial. Three studies (Nofal 2010, Mohamad 2013 and Shaheen 2015) were assessed to have unclear risk of bias.

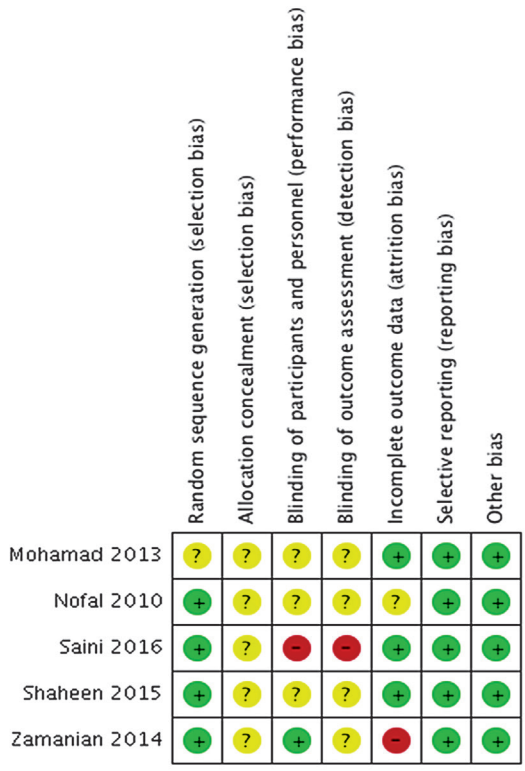

Figure 1. Risk of bias summary.

Detection bias was graded unclear for the studies of Mohamad 2013, Nofal 2010, Shaheen 2015 and Zamanian 2014 as there was no explicit statement as to whether the outcome assessors were blinded in the trials.

The Saini 2016 study was assessed to have a high risk of performance and detection bias since the study is an open label trial.

Attrition Bias

All the participants in the Mohamad 2013 and Shaheen 2015 studies completed the trial. The Zamanian 2014 study was assessed to have a high risk of attrition bias, as there was a computed large effect of dropouts. The Saini_2016 study was assessed to have a low risk of attrition bias since the dropouts did not have a large effect on the analysis.

Reporting Bias

All of the included studies were of low risk of bias because pre-specified outcomes were measured. All outcomes and adverse events were reported as stated by the articles.

Other Bias

Neither conflicts of interest nor any funding sources were declared by the included studies hence this parameter was assessed to be low risk of bias.

Effects of interventions

Data and Pooled Analyses

Four studies were included in the meta-analysis (Mohamad 2013, Nofal 2010, Shaheen 2015, Zamanian 2014). These studies compared intralesional MMR vaccine to placebo (normal saline) with Shaheen 2015 also comparing MMR to PPD. Effect estimates to the left of the vertical line imply benefit from the experimental group (intralesional MMR). There was a greater clearance of target warts in the intralesional MMR group as compared to intralesional saline or PPD with a risk ratio of 0.25 [95% CI 0.18, 0.35] at the end of the study period (Figure 2). There was no heterogeneity with I^2 =0.

Sub-group analysis was done with 4 studies comparing MMR to intralesional placebo/saline (Mohamad 2013, Nofal 2010, Shaheen 2015 and Zamanian 2014). Effect estimates to the left of the vertical line imply benefit from the experimental group (intralesional MMR). There was a greater clearance of target warts in the intralesional MMR group as compared to intralesional saline with a risk ratio of 0.24 [95% CI 0.18, 0.34] at the end of the study period (Figure 3). There was no heterogeneity between the compiled studies.

Another sub-group analysis was done with three studies (Mohamad 2013, Nofal 2010, Shaheen 2015) assessing the response in distant warts versus placebo. The Saini 2016 study was not included in the meta-analysis since the comparator was mechanical destruction. As seen in the forest plot (Figure 4), the intervention was beneficial as compared to placebo with a risk ratio of 0.28 (95% CI 0.08, 0.96) at the end of the study period. This study had high heterogeneity (I^2 =84%).

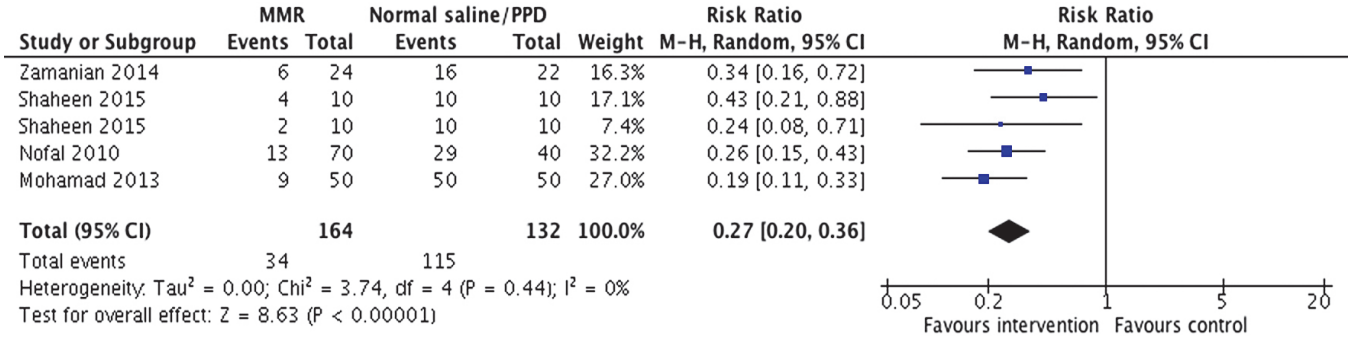

Figure 2. Forest plot of comparison of intralesional MMR versus placebo and PPD.

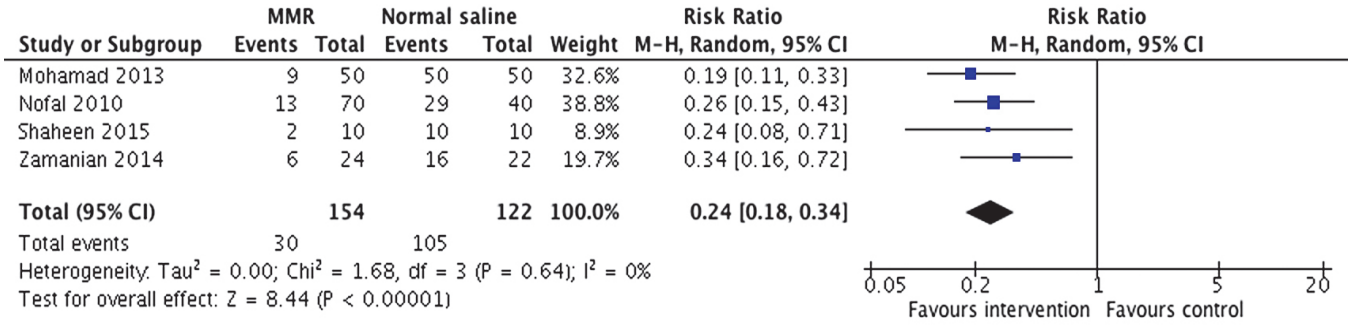

Figure 3. Forest plot of comparison of intralesional MMR versus placebo.

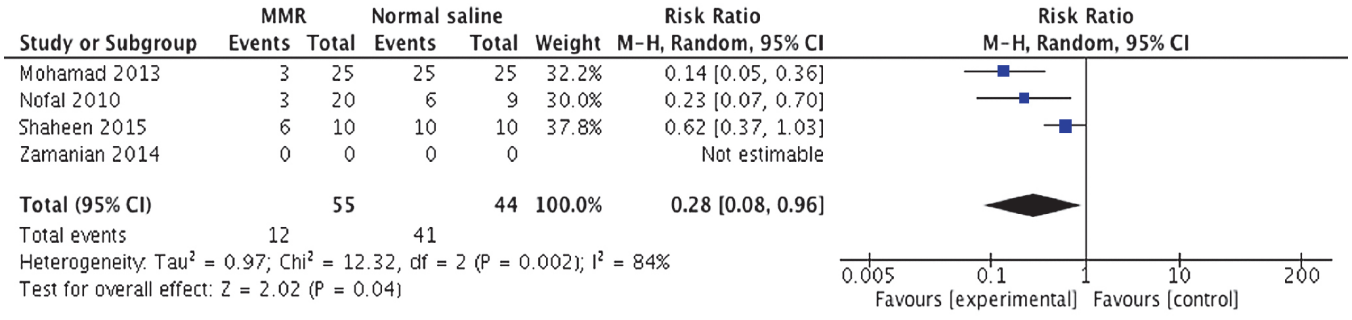

Figure 4. Forest plot of comparison of intralesional MMR versus placebo with treatment failure of distant lesions as outcome.

DISCUSSION

Summary of main results

Five randomized controlled trials were included in this review. These studies compared intralesional MMR to placebo (n=436). Four studies compared MMR to intralesional placebo or PPD. Three of the 4 studies also assessed clearance of distant warts using the intervention.

Trials were assessed to have moderate to high risk of bias. The study by Zamanian 2014 was said to have high risk of bias due to a computed large effect of dropouts thereby giving the study an overall rating of high risk of bias. The study by Saini 2016 also had a high risk of bias since it was an open label trial. The rest of the studies (Mohamad 2013, Nofal 2010 and Shaheen 2015) were said to have moderate risk of bias overall mostly due to unclear statement of blinding and allocation.

This review found that intralesional MMR was beneficial in the treatment of target cutaneous warts as compared to intralesional placebo and PPD. The pooled analysis showed a significant difference in the overall effect (P<0.00001) with no heterogeneity. For clearance of distant warts, this review found that intralesional MMR is also beneficial as compared to placebo. There was a significant difference in the overall effect (P=0.04) but analysis showed high heterogeneity (I^2 =84%). This could be explained by a small sample size of the studies that assessed clearance of distant warts and the differences in sample size between studies making the data inconsistent. Another possible reason for the high heterogeneity was that there is a difference between the amounts of MMR injected. For the Mohamad 2013 study, a constant 0.3mL intralesional MMR was injected as compared to the studies by Nofal 2010 and Shaheen 2015, where the amount of MMR injected was dependent on the size of the skin test reaction initially done.

Safety and recurrence rates were also taken note of. No recurrence was reported in the patients treated with intralesional MMR vaccine in the follow-up period designated per study. Side effects reported included pain, flu-like symptoms and erythema.

Overall completeness and application of evidence

All of the patients in the study were diagnosed with cutaneous warts. There were different types of warts tested in the different studies, plantar warts for Mohamad 2013, common warts for Nofal 2010 and different types for the remaining 3 studies. However, for the studies that had patients with different kinds of warts enrolled, only Shaheen et al reported that there was no statistically significant relation between the type of wart and the response to the intervention. Therefore, no generalizations could be made in this review in terms of response of specific types of warts to intralesional MMR. Response to distant warts was also assessed by 3 studies in this review, which may make treatment less costly and time-consuming to patients. The intervention may be offered as an alternative to those suffering from recalcitrant warts. In terms of population, majority of the participants in this review were from Egypt (3 studies versus 2 Indian studies by Zamanian and Saini et al.). All trials were able to address the primary and secondary outcome of this review. Efficacy of intralesional MMR as treatment for cutaneous warts, both target and distant, was measured by the decrease in size of the lesions to complete clearance and return of normal skin markings. Safety and side effects were reported by the participants with no significant adverse events reported. The follow-up period of 3 and 6 months however may not be sufficient to assess the long-term effect of intralesional immunotherapy with MMR vaccine, as there were reports in the studies of ongoing reduction in size of lesions even on the follow-up period (no active intervention being done).

Quality of evidence

Studies were assessed to have a moderate risk of bias for 3 studies and a high risk of bias for the Zamanian 2014 and Saini 2016 study. None of the included trials were of low risk of bias. In terms of reported outcomes, the quality of evidence was further assessed by exploring inconsistency, indirectness and imprecision as outlined in the GRADEpro software. Summary of findings are shown in Table 3.

Inconsistency

Intralesional MMR vaccine versus placebo on target warts had a computed I^2 value of 0% denoting no heterogeneity with a P-value of P<0.00001 which was significant. Intralesional MMR vaccine versus placebo in distant warts showed high heterogeneity with an I^2 value of 84%. This may be explained by the small sample size of the studies that assessed effect in distant warts and difference in sample sizes between groups.

Indirectness

Indirectness was measured in terms of generalizability and external validity by assessment of the PICOM. This was deemed not serious for the outcome of complete clearance of distant and target warts.

Imprecision

A large sample size was used in the comparison between intralesional MMR vaccine on target warts and

Table 3. Summary of findings table

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality
	Risk with placebo	Risk with MMR			
Complete resolution	861 per 1000	207 per 1000 (155 to 301)	RR 0.24 (0.18 to 0.35)	276 (4 RCTs)	High
Distant wart	932 per 1000	261 per 1000 (75 to 895)	RR 0.28 (0.08 to 0.96)	99 (3 RCTs)	Low

placebo and the confidence interval computed was not wide thereby assessing this to be not serious. This is in contrast to the effect of the intervention on distant lesions where there was a very small sample size and a wide confidence interval thereby assessing this to be serious and thus downgrading the quality of evidence.

Other considerations

Other considerations in determining the quality of evidence include undetected publication bias; no presence of large effect, and presence of a dose response gradient and plausible confounding that would reduce demonstrated effect.

Agreement and disagreement with other studies or reviews

There are limited studies on intralesional MMR vaccine that are randomized controlled trials. Most studies compared this treatment on target and distant warts to placebo and fewer studies have been done comparing it to the current standard of treatment and to other forms of intralesional immunotherapy. Most of the studies, especially those that demonstrated effects on distant lesions, have small sample sizes, which may explain the high heterogeneity.

CONCLUSION

Implication for practice

The quality of the current evidence for intralesional MMR vaccine in target warts is high while evidence for MMR vaccine on distant warts is low. However, as seen in this review, intralesional MMR vaccine is effective in clearing target and distant warts and also has a significant effect in reducing the size of the lesions in 6-10 weeks. It is a generally safe therapeutic option with low recurrence rates and still with observed effect (reduction in size) even on follow-up. This may be a good alternative to current treatment modalities for cutaneous warts, especially the recalcitrant ones, and has lower potential for scarring and trauma.

Implication for research

Type of study

Future trials should be controlled trials with clearly stated and properly executed method of randomization and allocation concealment. Triple-blinded trials may also be done to ensure lower chances of bias in the assessment of response and side effects. Follow-up rate should also be longer to monitor recurrence and evaluate effect even after active intervention.

Intervention

A protocol wherein a standardized amount of MMR vaccine is to be injected with evaluation of distant warts. Also, studies comparing intralesional MMR vaccine to current standard of treatment and other forms of intralesional immunotherapy may be conducted.

Outcome

As the study only employed assessment of complete clearance of warts as an outcome, further studies and analyses can also be done taking into account the reduction in size of the lesions during the follow-up period. More studies can also be done on a larger population (greater sample size) to evaluate the effect of the intervention to distant warts and on recurrence rates. A more quantitative manner of reporting for side effects such as pain score may also be utilized.

Disclaimer

The views expressed in this article are the authors' own and do not reflect the views of the institution.

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