

Title: A COMPARATIVE STUDY TO ASSESS EFFICACY OF INTRALESIONAL
MMR (MEASLES, MUMPS, RUBELLA) VACCINE AND INTRALESIONAL
VITAMIN D3 IN TREATMENT OF WARTS

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SUMMARY OF POST GRADUATE THESIS PROTOCOL

- 1. Study title** : A comparative study to assess efficacy of Intralesional MMR (Measles, Mumps, Rubella) vaccine and Intralesional Vitamin D3 in treatment of Warts
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- 7. Rationale of the research** : As per my literature search,
1. No previous studies on immunotherapy in wart have been conducted in our country
 2. No comparative studies have been done to compare IL MMR and IL vitamin D3 in treatment of wart hence we aim to establish efficacy of each and compare the two in our country
- 8. Objectives** : **Primary Objectives:**

1. To determine the efficacy of IL MMR vaccine in the treatment of Wart
2. To determine the efficacy of IL vitamin D in the treatment of wart
3. To compare the efficacy of IL MMR vaccine and IL Vitamin D

Secondary Objectives:

1. To determine the frequency of patients with different types of warts visiting Dermatology outpatient department of BPKIHS
2. To determine the side effects of IL MMR vaccine and IL Vitamin D in treatment of wart
3. To determine Dermatology life quality index (DLQI) in wart patients.

9. Research Hypothesis : Null Hypotheses (H₀):

IL MMR vaccine is not better than IL Vitamin D in the treatment of wart

Alternative hypothesis:

IL MMR vaccine is better than IL Vitamin D in the treatment of wart

10. Material & Methods:

(a) Whether study involves Human/animals or both : Human only

(b) Population/ participants : Patients with warts visiting Dermatology outpatient department

(c) Type of study design : Prospective comparative longitudinal Study

(d) Setting : Outpatient Department of Dermatology and Venereology, BPKIHS

(e) Sample Selection criteria:

(i) Inclusion Criteria :

1. Clinically diagnosed patients who have more than three warts or single wart in difficult to treat sites (periungual, palms and soles)
2. Age > 12 years

(ii) Exclusion Criteria :

1. Patients not under any systemic or topical treatment of warts for the last four weeks
2. Patients with a past history of an allergic response to MMR or any other vaccine or Vitamin D
3. Patients with current acute febrile illness or any bacterial infection
4. Immunosuppressed patients
5. Pregnant or lactating women
6. Patients having a past history of asthma, allergic skin disorders or convulsions
7. Patients with keloidal tendency
8. Patient refusal for consent
9. Treating physician's decision to give other treatment modality
10. Patients with hypervitaminosis D, muscle weakness, bone pain, altered sensorium

(f) Expected sample size : 60 (30 in each group)

(g) Control groups : not applicable

(h) Probable duration of study : one year

(i) Parameter/Variables to be measured: Age, sex, race, occupation, number of warts, site of warts, response rate, DLQI

(j) Outcome measures : Response rate of warts to IL MMR and IL Vitamin D3

(k) Statistical methods to be employed :

a. **Data handling:** Data were entered in Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA) and statistical analysis was done using Statistical Package for the Social Sciences 10.5 version (Chicago, Inc)

b. **Coding:** Alpha numerical code was used

c. **Monitoring:** Data was entered after every day of work and supervised by guide.

d. **Statistical analysis:** will be conducted as per both per-protocol and intention-to treat population (defined as all enrolled patients to whom study drug will be given; with the last observation carried forward) basis using two sided tests.

For *descriptive statistics*, percentage, mean, S.D., median, and minimum, maximum will be calculated along with graphical and tabular presentation.

For *inferential statistics*, statistical methods that will be used are as follow

1. Chi square test and Fisher's exact test to compare the categorical data between the groups.

2. Paired t test for comparing normally distributed continuous variables (pretreatment and post treatment DLQI) at different time point within the groups.

3. Mann- Whitney U test to compare the not normally distributed variables (age,

duration of illness, size, number)

4. Kaplan–Meier curves to compare the response rate (complete, excellent, good or poor response) on each follow up visit (week 3, 6, 9, 12) between the groups.

Test of significance will be considered when value of $p \leq 0.05$.

(l) Ethical clearance : Will be obtained from the Institutional Review Committee (IRC), BPKIHS and Nepal Health Research Council (NHRC)

(m) Permission to use copyright questionnaire/Proforma : N/A

11. For Intervention trial

a. Permission from Drug Controller of Nepal: not required

b. Safety measure :will be applied

c. Plan to withdraw :As per the decision of treating physician

12. Maintain the confidentiality of subject : Yes

13. References : attached

14. Whether available resources are adequate: adequate

15. Other resources needed : not needed

16. Cost involved (Approx in NRS)

a. Investigations :60,000 (approximate)

b. Surgery :NA

c. Drugs :64,500 (approximate)

Group A- MMR cost × number of participants × number of sessions per patient

$$=350 \times 30 \times 5$$

$$=52,500$$

Group B- Vitamin D cost × number of participants × number of sessions per patient

$$=80 \times 30 \times 5$$

$$=12,000$$

Total cost = 64,500

Both MMR and Vitamin D are easily available in local pharmacy.

17. Who will bear the cost of the requirements? Patient

18. ANNEXURE:

a. Participants record form (clinical data sheet): Attached

b. Participant Information sheet

i. Attached English

c. Participant Informed consent form

i. Attached English

ABBREVIATIONS

ANOVA	-	Analysis of Variance
BCG	-	Bacillus Calmette Guerin
BPKIHS	-	BP Koirala Institute of Health Sciences
DLQI	-	Dermatology Life Quality Index
DNA	-	Deoxyribonucleic Acid
DNCB	-	Dinitrochlorobenzene
DPCP	-	Diphenylcyclopropenone
G	-	Gauze
HPV	-	Human Papilloma Virus
IOE	-	Institute of Medicine
IFN	-	Interferon
IL	-	Intralesional, Interleukin
IRC	-	Institutional Review Committee
MD	-	Doctor of Medicine
MMR	-	Measles, Mumps, Rubella
NA	-	Not applicable
NHRC	-	Nepal Health Research Council
NK	-	Natural Killer
OPD	-	Outpatient Department
QoL	-	Quality of Life
RCT	-	Random Control Trial
SADBE	-	Squaric acid dibutyl ester
TEIB	-	Triethyleneiminobenzoquinone
Th	-	T- helper
TLR	-	Toll like receptor
VAS	-	Visual Analogue scale
VDR	-	Vitamin D receptor
VDRA	-	Vitamin D receptor activator

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INTRODUCTION

Warts are papulonodular epidermal lesions with a horny or papillomatous surface caused due to infection by human papillomavirus (HPV).¹

Cutaneous warts occur in 7% to 10% of the general population, with a maximum incidence between the ages of 12 and 16 years.² Warts can persist as it is for years and then spontaneously clear at any time from a few months to a few years. In children, clearance can occur even after only a few months, with 50% at 1 year and about 65%–78% by 2 years.^{2,3} The rate of clearance is influenced by factors like virus strain, host immune status, extent, and duration of warts⁴

HPVs are ubiquitous, epitheliotropic non-enveloped small double-stranded DNA viruses.⁵ Over 150 types of papillomavirus have been identified based on DNA studies and serological detection of type-specific antibodies against HPV capsid antigens.^{1,6} Among them verruca vulgaris or common warts are usually caused by Human Papilloma Virus (HPV) types 1, 2, 4, 27 or 57, and plane warts by HPV types 3 or 10.²

The transmission of warts occurs from direct contact or indirectly via fomites. Usually, warts spread in swimming pools and bathrooms as the skin is macerated and is more prone to minor abrasions and infections thus serving as conduits for HPV to the basal keratinocytes, the primary targets for HPV infection.^{2,6} There they undergo a latent phase of slow replication and then induce epidermal hyperplasia and hyperkeratosis as the epidermis grows superficially.⁷

The destructive therapies in treatment of wart include salicylic acid, trichloroacetic acid, cryotherapy, silver nitrate, phenol, cantharidin, surgical interventions and lasers; antiproliferative agents include bleomycin, vitamin D analogs, podophyllin, podophyllotoxin, and 5-fluorouracil; antiviral agents include cidofovir and retinoids.² Other modalities include hypnotherapy, acupuncture, local hyperthermia, therapeutic vaccination, and combinations of the previous agents.⁸

Destructive therapies are usually uncomfortable, require multiple sessions and individual treatment of each wart, and are often associated with variable efficacy, high recurrence, and significant adverse effects such as scarring.⁹ Hence immunotherapy is becoming more and more popular, especially in the treatment of refractory cutaneous and genital warts. These include various topical, intralesional (IL), and systemic agents.¹⁰

Immunotherapy is defined as a type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Immunotherapy can affect the immune system in general or can be cell-specific.¹⁰

Immunotherapeutic agents include:

1. Prophylactic vaccination using viral antigens
2. Therapeutic vaccination using viral antigens
3. Pro-inflammatory cytokines and tumor destroyers (interferon)
4. Immune enhancement
 - a. Topical (imiquimod)
 - b. Systemic (cimetidine, levamisole, zinc sulfate)

5. Induction of delayed (cellular) hypersensitivity
 - a. Intradermal (tuberculin, candidin, trichophyton, mumps antigen, BCG, Vitamin D)
 - b. Topical (DNCB, DPCP, SADBE, TEIB)
6. Combination treatment ^{11,12}

The exact mechanism of immunotherapy is not yet known but it is believed that the injection to the HPV-infected tissue induces a strong nonspecific pro-inflammatory signal and attracts the antigen-presenting cells. This is associated with the release of cytokines such as IL-2, IL-8, IL-12, IL-18, tumor necrosis factor- α , and interferon- γ .^{13,14} This then promotes a Th1 cytokine response which leads to the activation of cytotoxic T cells and natural killer cells i.e. delayed-type hypersensitivity reaction leading to the eradication of the HPV-infected cells.^{15,16} Furthermore, the trauma of the injection may also cause a resolution in previously sensitized individuals.¹⁷ Since intralesional antigen immunotherapy enhances recognition of the virus by the immune system it causes clearance of both treated and untreated lesions and helps to prevent future clinical infection through induction of long-term acquired immunity to HPV.¹³

Measles, Mumps Rubella (MMR) vaccine is included in immunization schedule so pre-sensitization skin test is not needed as all patients are expected to be immune.⁵ In 1989, monovalent measles vaccine was introduced in Nepal for vaccination of infants at age nine months. In 2013, measles-rubella (MR) vaccine was introduced into the national routine immunization schedule and replaced monovalent measles vaccine.¹⁸ The presence of three different antigens in MMR

increases the sensitivity to the injected antigen and decreases the likelihood of anergy.⁸ Side effects of MMR include pain during injection, flu-like symptoms, pruritus and burning sensation.^{19,20}

Intralesional (IL) vitamin D is a novel addition to therapies in warts as it is a simple, effective, well-tolerable, and inexpensive method with negligible local and systemic side effects^{21,22}

Side effects of Vitamin D3 include transient mild to moderate pain, edema at the site of injection, resolving within 1 week mild erythema.²² Further it would be safer to measure serum vitamin D and calcium levels before and after intralesional vitamin D treatment to prevent possible hypervitaminosis D.²³

Vitamin D3 acts on the principle of immunotherapy by stimulating cell-mediated immunity²¹ In addition, it is also claimed to regulate epidermal cell differentiation and proliferation and may modulate cytokine production through its action upon vitamin D receptors(VDRs).²² VDRs are present in the keratinocytes, melanocytes, fibroblasts, and immune system cells of the skin. Activation of Toll-like receptor (TLR) of human macrophages up-regulates the expression of vitamin D receptor and vitamin D1- hydroxylase genes, leading to induction of the antimicrobial peptide like thymic stromal, lymphopoietin and cathelicidin. ^{24,12} It also reduces the synthesis of IL1a and IL6 resulting in decreased inflammation. VDR activators (VDRAs) have been shown to inhibit cell replication and have immunomodulatory properties.²⁵

It is supposed that combining intralesional immunotherapy with a destructive treatment method might enhance the efficacy, shorten the treatment duration, and reduce the possible side effects.⁷

RATIONALE OF THE STUDY

Intralesional Immunotherapy is an emerging method of treatment of warts in which injection in a single wart causes the resolution of distant warts as well. Compared to other destructive modalities, it is more effective and comfortable for the patient as it obviates the need for individual treatment of each wart. In addition it has a lower rate of recurrence, avoids adverse effects such as scarring, is more cost-effective in multiple warts and decreases the time a physician has to spend on each patient. Further both injection MMR and Vitamin D3 are readily available as compared to other immunotherapeutic agents like PPD and candida antigen.

IL MMR vaccine has been used for a longer time than IL vitamin D and there are more comparative studies showing efficacy of MMR vaccine with rates of clearance ranging from 70.4% to 82.4%.^{26,27} The clearance rates for IL vitamin D range from 40% to 90%.^{22,28} As per Committee to Review Adverse Effects of Vaccines; Institute of Medicine (IOE), there is evidence of causal relationship between MMR vaccine and measles inclusion body encephalitis in individuals with demonstrated immunodeficiencies.²⁹ Hence immunodeficiency is one of the exclusion criteria for MMR administration.

The advantages of vitamin D over MMR vaccine are cost-effectiveness, non-requirement of maintenance of cold chain, easy availability, and feasibility of use in immunosuppressed patients.

As per Institute of Medicine (IOM), the tolerable upper intake of vitamin D is 4000 IU/day for anyone older than 9 years such that annual maximum dose will be 1,460,000 IU.³⁰ The total amount of vitamin D that we will be administering will be

1,500,000 IU. Furthermore, since we are giving it intralesionally systemic absorption is likely to be low although data on exact amount of IL vitamin D that gets absorbed systemically is not available. In other studies, patients have been evaluated clinically for signs and symptoms of hypervitaminosis D however, no signs of toxicity were observed.^{12,21,22,23,28,31}

As per my literature search,

1. No previous studies on immunotherapy in wart have been conducted in our country
2. No comparative studies have been done to compare IL MMR and IL vitamin D3 in treatment of wart hence we aim to establish efficacy of each and compare the two.

REVIEW OF LITERATURE

Warts are common skin conditions resulting from infection of keratinocytes by human papillomavirus (HPV)¹. The development of epidermal thickening and hyperkeratinization occurs following infection at the basal layer and clonal proliferation, which eventually results in a visible wart, weeks or even months later.²

Many studies have documented the prevalence of cutaneous warts in children 9–13, ranging widely from 3.3% in the USA to 33% in the Netherlands.³² In a study conducted by Liu et al it was found that 1.4% of college students were affected with warts on their hands and/or feet.³³ This frequency is estimated to be 7 to 10% of the population in Europe and in the United States.³⁴ According to age group, the prevalence of warts is highest in school-aged children, followed by adults then preschool-aged children.¹ In Great Britain, 6.5% of the school children had plantar warts, and 9.5% had warts at other sites.³⁴

Most large studies have found no evidence of a sex difference in wart prevalence. However, a female preponderance is seen in the frequency of plantar warts.³⁴ In the East Anglia survey, 8.4% of females had plantar warts compared to 4.9% of males.¹

The use of swimming pools, sports clubs, gymnasiums, or public baths increases the risk of contracting plantar warts. School children and young adults constitute a high epidemiologic risk population and an important source of the dissemination of cutaneous warts since their families are more often infected up to 50% of cases.

Among butchers and workers in the meat-handling industry, the prevalence of warts on the hands is much higher than in the general population as their hands are subjected to many traumatisms. Other factors thought to be responsible are cold, permanently humid conditions, in which workers often use the same tools and working tables.³⁴

Classification of warts³⁵

Cutaneous warts can be classified in relation to the clinical morphology and the type of infecting HPV as follows:

1. Common wart (*Verruca Vulgaris*)

- a. typical or exophytic
- b. mosaic
- c. endophytic,
- d. papillomatous or filiform

2. Plane and intermediate warts

3. Myrmecia

4. Pigmented plaques

.

- 1. Typical common warts are exophytic, i.e. elevated. Their surface is rough irregular, hyperkeratotic, with minute papillary projections.
- 2. Mosaic warts appear usually in plantar locations. They are superficial, only slightly raised above the skin level, hyperkeratotic, multiple, confluent with polygonal outlines, and painless.

3. Endophytic common warts appear characteristically in palmar and plantar localizations. Deep plantar common warts are most often multiple, painless, with a slightly raised, hyperkeratotic surface. Even for experienced dermatologists, the differentiation between myrmecias and deep common warts is difficult.
4. Papillomatous common warts are usually less typical, resembling papillomas, localized most often on the face, head, neck, in the folds.
5. Plane warts are slightly raised above the skin level, smaller than common warts, with flatter, smoother surfaces and irregular outline. Intermediate warts, a term applied to lesions that cannot be classified as common or plane warts, combine clinical features of both.
6. Myrmecia warts, if in plantar location, are often referred to as deep plantar warts. They may also be palmar and the warts are endophytic, deep, and more often single. Characteristic findings include small bleeding points and punctate dots appearing after trimming off the hard horny covering.

A few atypical warts, example, pigmented plaques in immunosuppressed patients, remain unclassified until more is known about the incidence and natural history.³⁵

Intralesional MMR vaccine

The mechanism of action of intralesional MMR immunotherapy is still an enigma. Some authors hypothesize that it acts through the induction of a strong nonspecific inflammatory response against the HPV-infected cells.^{19,20} It has also been suggested that the trauma itself may cause wart clearance in previously

sensitized individuals.¹⁵ The cytokines produced by immune system such as interleukin (IL)-2, IL-4, IL-5, IL-8, interferon (IFN)- γ and tumor necrosis factor (TNF)- α stimulate a strong immune response against HPV may be another possible mechanism of action.²¹ Another author reports that the response to antigen injection was associated with the proliferation of peripheral blood mononuclear cells that promotes Th1 cytokines including IFN- γ and IL 2, which further activate cytotoxic T cells and natural killer (NK) cells that eradicate HPV-infected cells.^{17,26}

Subjects can be tested for existing immunity by intradermal injection of 0.1 mL of MMR vaccine into the skin of the forearm. Determination of a positive reaction requires erythema and induration of at least 5 mm in diameter within 48–72 hours. Patients reactive to the skin test are labelled responders and IL MMR is more effective in them.²⁰

Nofal A et al conducted a randomized controlled trial (RCT) with 135 patients of which 85 patients received the MMR vaccine and 50 received Normal saline as control. Both treatment groups were injected in single largest wart at 2 weekly intervals until complete clearance for a maximum of 5 treatment and were followed up bimonthly for 6 months. In the MMR group, complete response was achieved in 80% and 84.6% of patients presenting with recalcitrant and multiple warts respectively. No recurrence was observed in the MMR group and side effects included pain during injection and flu-like symptoms.²⁰

Author	Setting	Type of Study	Sample size	Type of wart	Percentage of complete clearance
Nofal A and Nofal E, 2010 ²⁰	Zagazig University, Egypt	Randomized controlled trial	135	Common warts	Recalcitrant wart-80% Multiple Wart-84.6%
Nofal A et al. 2015 ⁸	Zagazig University, Egypt	Prospective	65	recalcitrant wart	63%
Naseem R and Aamir S, 2013 ³⁶	Federal postgraduate medical Institute & Sheikh Zayed Hospital, Lahore, Pakistan	Prospective	170	Common warts	81.3%
Mohamad NS et al, 2013 ³⁷	Alexandria Main University Hospital, Egypt	Quasi experimental trial	100	Plantar wart	82%
Shah A et al, 2016 ³⁸	NHL Municipal Medical College, Ahmedabad, Gujarat, India	Prospective study	50	Common warts	72%
Raju J et al, 2016 ³⁹	Mysore Medical College & Research Institute, Mysore, India	Prospective study	27	Common warts	70.4%
Rohit V et al, 2017 ⁴⁰	Chalmeda Anand Rao Institute of Medical Sciences, Telangana, India.	Case-control study	50	Common warts	72%
Chauhan PS et al, 2017 ²⁷	Dr.R.P. Govt. Medical College, Kangra (Tanda), Himachal Pradesh, India	Prospective study	51	Common warts	82.4%

Table 1: Comparison of different studies on IL MMR in warts

Again in 2015, **Nofal et al** conducted a similar study in recalcitrant wart where they included sixty-five patients. Recalcitrant warts were defined as warts persistent for more than two years despite treatment with at least two different modalities. Distant warts were defined as warts at different anatomic sites away from the treated wart. Complete clearance of the lesions was observed in 41 patients (63%), partial response in 15 patients (23%), and no response in nine patients (14%). Complete response was demonstrated in 74.5% of those presenting with distant warts. Side effects were mild and insignificant in the form of pain during injection, itching, erythema, and edema at the site of injection and flu-like symptoms. Recurrence was detected in two patients only⁸

Similarly in a study conducted by **Naseem, Aamir** in 2013 there were total 170 patients and final efficacy came as 81.3% which shows that a large number (122) of patients show complete response to the MMR vaccination.³⁶

Nagat Sobhy Mohamad, et al observed that the response of the target wart, MMR- treated group showed a significantly higher rate of complete clearance compared with the control group (82% versus 0% respectively). The rate of partial response was 6% versus 30%, and the rate of no response was 12% versus 70%, respectively. Regarding the response of untreated distant warts, the MMR-treated group showed 86.9% complete and 13.1% partial clearance of the warts whereas the control group showed 100% no response.³⁷

In a prospective study conducted in the Dermatology outpatient department of V.S Hospital, Ahmedabad by **Shah A et al** over a period of one year patients received

intralesional MMR vaccine 0.5ml into a single wart or the largest wart in case of multiple lesions at an interval of two weeks for three treatments. The response was evaluated as 0-49% as no response, 50-99% as partial response and 100% as complete response. Follow up was made every 02 weeks for 06 weeks and then monthly for 06 months to detect any recurrence. They found complete response was seen in 36 (72%), partial response in 08 (16%) and no response in 06 (12%) patients. No recurrence was observed. Pain at the site of injection in 18 (36%) and the flu like symptoms in 02 (04%) patients were observed. ³⁸

In 2016 **J Raju et al** injected MMR vaccine into the largest single wart intralesionally and gave subsequent injections every 2 weeks apart for about 3 to 5 times and obtained complete remission of warts in 70.4% of patients, partial remission in 22.2% and no response in 7.4% of patients. ³⁹

Vontela R et al observed complete clearance in 72% patients and partial clearance in 16% of patients receiving the MMR vaccine. No response is seen in 12% of patients. The recurrence rate during the 6 months follow up period is 12%. Pain during injection was noted in 60% of patients without any other adverse effects in the treated patients. The mean duration taken to show the complete clearance of the lesions is 9 weeks⁴⁰

In 2017 **Chauhan et al** injected 0.25 mL MMR vaccine intralesionally in the largest wart and repeated at 2-week interval until complete clearance or a maximum of five doses. They evaluated outcome as complete clearance, excellent, good, or unsatisfactory response on a visual analog scale at every visit

and at 4 and 8 weeks, thereafter by comparing baseline clinical photographs. They used a Likert scale for patient satisfaction level assessment similarly. Out of 51 patients who completed the study 42 (82.4%) of them showed complete clearance of warts and 9 (17.6%) patients showed good or unsatisfactory response. In 4 (7.8%) patients, warts subsided completely after one dose itself. The four patients showing an excellent response after five doses initially also continued to improve during a follow-up period of 8 weeks. Except for injection site pain, no adverse effects were noted. There was no recurrence of warts among them.²⁷

Intralesional Vitamin D3

Vitamin D3 acts on the principle of immunotherapy by stimulating cell-mediated immunity²¹ Vitamin D is also claimed to regulate epidermal cell differentiation and proliferation and may modulate cytokine production through its action upon vitamin D receptors.²² The vitamin D receptors are present in the keratinocytes, melanocytes, fibroblasts, and immune system cells of the skin. Activation of Toll-like receptor (TLR) of human macrophages up-regulates the expression of vitamin D receptor and vitamin D1- hydroxylase genes, leading to induction of the antimicrobial peptide²⁴ like thymic stromal, lymphopoietin and cathelicidin. It also reduces the synthesis of IL 1a and IL6 resulting in decreased inflammation. VDR activators (VDRA) have been shown to inhibit cell replication and have immunomodulatory properties.²⁵

Author	Setting	Type of study	Sample size	Type of wart	Percentage of complete clearance	Recurrence
Aktaş et al. 2016 ²³	Different hospitals of Turkey	Prospective study	20	Common warts	80%	No
Jakhar, Kaur, and Misri 2018 ²¹	NDMC Medical College and Hindu Rao Hospital, Delhi	case report	1	Periungal wart	-	Not mentioned
Raghukumar et al. 2017 ²²	Hassan Institute of Medical Sciences, Hassan, Karnataka state, India	Prospective study	64	recalcitrant warts	90%	2(3.7%)
Kareem et al. 2019 ¹²	Al-Azhar University, Cairo, Egypt	RCT	50	Common warts	40%	Not mentioned
El-Taweel, Salem, and Allam 2019 ²⁸	Benha University, Egypt	Prospective study	20	Common warts	40%	No
Manjunath K et al. 2019 ³¹	Mandya Institute of Medical Sciences, Mandya, Karnataka, India	Prospective study	42	Multiple warts	78.57%	1(5.26%)

Table no. 2: Comparison of studies on IL Vitamin D3 in Warts

Aktas et al conducted study with 20 patients with single or multiple plantar warts. Vitamin D3 (0.2 mL, 7.5 mg/mL) was injected into the base of the warts after prilocaine (0.1 mL, 20 mg/mL) injection. A maximum of 5 warts were treated in 1 session, with a maximum 2 injections performed at 4-week intervals. In total, 16 of 20 patients (80%) showed complete resolution of warts, and 1 patient showed partial resolution. Three patients failed to show any response. No recurrence or serious adverse effects were observed. ²³

In a case report done by **Jakhar, Kaur, and Misri** in 2018, the injection was given at a dose of 0.1 mL/cm² just beneath the wart. A maximum of 0.4 mL was used in a single session in cases of multiple warts. The session was repeated at 2-week intervals for a maximum of 4 sessions or complete resolution of warts, whichever is earlier. The resolution of warts typically started in 7 to 10 days, and warts are shed spontaneously within 4 to 6 weeks. The only side effect was pain during injection, which was minimized with a dose of lidocaine before injection with vitamin D3. Two to 4 sessions are usually required on average for complete cure.

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Raghukumar et al. conducted a study in 2017 in 64 patients with recalcitrant warts. Complete response with IL vitamin D was seen in 54 of 60 (90%), partial response in 4 of 60 (6.66%), and no response in 2 of 60 (3.33%). The average number of injections required to achieve a complete resolution was 3.66. Complete resolution of distant warts was noticed in all patients. ²²

Kareem et al. conducted RCT in 50 patients who were divided into two groups: thirty patients as cases group who received an intralesional injection of 0.2 ml of vitamin D3 (300.000 IU) and another twenty patients as a control group who were injected with normal saline solution. Standardized photographs were taken before, one month and three months after the procedure. The degree of the response was classified into complete, partial and no response. Complete clearance of the target injected warts was seen in 40% of patients in the cases group and 5% of patients in the control group ($P \leq 0.001$) that was statistically significant.¹²

Similarly, in a study conducted by **EI-Taweel et al.** 20 patients with verruca vulgaris and deep palmoplantar warts were included. Forty percent of the lesions treated with IL vitamin D3 showed complete clearance and the rate of distant wart response was 17.65%. Among different demographic and clinical variables in the studied patients, smoking and older age seemed to decrease the therapeutic response²⁸

In a prospective study conducted by **Shilpa et al** on 2019, 33 of 42 patients (78.57%) showed a complete response, 6 patients (14.28%) showed moderate response and three patients (7.14%) showed mild response with IL vitamin D3. Recurrence was observed in one patient with the palmoplantar wart. No serious adverse effects were reported.³¹

OBJECTIVES

Primary Objectives:

1. To determine the efficacy of IL MMR vaccine in the treatment of Wart
2. To determine the efficacy of IL vitamin D in the treatment of wart
3. To compare the efficacy of IL MMR vaccine and IL Vitamin D

Secondary Objective:

1. To determine the clinical and demographic profile of patients with different types of warts visiting Dermatology outpatient department of BPKIHS
2. To determine the side effects of IL MMR vaccine and IL Vitamin D in treatment of wart
3. To determine Dermatology life quality index (DLQI) in wart patients.

RESEARCH HYPOTHESIS

Null Hypotheses (H0):

IL MMR vaccine is not better than IL Vitamin D in the treatment of wart

Alternative hypothesis:

IL MMR vaccine is better than IL Vitamin D in the treatment of wart

Operational definition

Wart – clinical diagnosis made by a dermatologist

Grades of clinical improvement	Definition	VAS score
Complete response	Complete disappearance of warts including distant ones and skin texture at the site is restored to normal	100%
Excellent response	Reduction in size and number including distant ones and few residual warts still visible	75–99%
Good response	Some reduction in size only including that of distant ones but no decrease in number of warts	50-74%
Poor or no response	No significant change in size and number of warts	0–49%
Recurrence	Recurrence during the study period	

Table no. 3 : Patient and physician global assessment using visual analog scale score²⁷

MATERIALS AND METHODOLOGY

Materials:

The study population will be all patients clinically diagnosed with warts visiting the Dermatology outpatient department of BPKIHS, Dharan.

Study design:

A Prospective comparative longitudinal study

Study Period:

The probable duration of the study will be one year after approval from the Institutional Review Committee and Nepal Health Research Council (NHRC)

Ethical Clearance

Ethical clearance will be taken from Institutional Review Committee (IRC), BPKIHS and Nepal Health Research Council (NHRC).

Conflict of interest: None

Sampling Technique: Census method with all consecutive patients meeting inclusion criteria for initial 6 months

Inclusion criteria

1. Clinically diagnosed patients who have more than three warts or single wart in difficult to treat sites (periungual, palms and soles)
2. Age \geq 12 years

Exclusion criteria

1. Patients under any systemic or topical treatment of warts for the last 4 weeks
2. Patients with a past history of an allergic response to MMR or any other vaccine or Vitamin D
3. Patients with current acute febrile illness or any bacterial infection
4. Immunosuppressed patients
5. Pregnant or lactating women
6. Patients having a past history of asthma, allergic skin disorders or convulsions
7. Patients with keloidal tendency
8. Patient refusal for consent
9. Treating physician's decision to give other modality of treatment
10. Patients with hypervitaminosis D, muscle weakness, bone pain, altered sensorium

Sample size

The study considers a 95% confidence interval, 80% power to estimate sample size. According to the literature review, it was found that 84.6% and 40% improvement were seen with IL MMR and IL Vitamin D respectively.^{20,12}

Now using the sample size estimation formula for 2 proportion

Now using the sample size estimation formula for 2 proportion

$$n = \frac{2p(1-p) (Z\beta + Z\alpha/2)^2}{(p_1 - p_2)^2}$$

$$(p_1 - p_2)$$

2

n= sample size for each group

$$p_1 = 0.846$$

$$p_2 = 0.40$$

$$p = (p_1 + p_2)/2$$

$$Z_{\alpha/2} = 1.96 \text{ at } 95\% \text{ CI}$$

$$Z_{\beta} = 0.842 \text{ at } 80\% \text{ power}$$

Using above formula, $n = 18.54$

Considering loss of follow up, sample size in each group = 30

Total sample size = **60**

Methodology

Based on the computer generated random number table, patients will be assigned to either Group A or Group B once they come to OPD. Informed consent will be taken. After that detailed information of all the patients satisfying inclusion criteria will be recorded in preset pro forma. This will include personal data, past history, medical history, drug history, clinical data like site, size, number, distribution of lesions. History of muscle weakness, bone pain, altered sensorium, anaphylaxis and immunosuppression will also be taken. In patients of group B serum vitamin D level will be measured after 20 days of 3rd dose and 1 month after the last dose to ensure safe monitoring. Photographs of the lesions will be taken before the first treatment session, in every treatment session and 3 months after last session.

Group A

Freeze-dried MMR vaccine single-use vials stored at 2°C–8°C will be reconstituted with 0.5 mL of provided diluent (distilled water) as per manufacturer's instruction immediately before intralesional use. If reconstituted vaccine is not used within 8 hours it must be discarded.³⁷ All Group A patients will

receive intralesional injection of upto 0.5 mL of reconstituted MMR vaccine into a single or a maximum of 5 warts at a time in case of multiple warts with 31 G insulin syringe with beveled edge facing upward. Amount of injection on each wart will depend on the size of each wart. The intralesional injection will be given every three weeks for a maximum of 5 doses or until complete resolution, whichever is earlier.⁵

Group B

All Group B patients will receive a maximum of 0.5 mL Inj. Vitamin D3 (600,000 IU; 15mg/ml) in each session after injection of IL lignocaine with 31 G insulin syringe. In cases of multiple warts, a maximum of 5 warts will be injected at a time. Amount of injection on each wart will depend on the size of each wart. The session will be done at 3 weekly intervals for a maximum of 5 sessions or until complete resolution of warts, whichever is earlier.²²

Patient and physician global assessment using 'Visual Analog Scale score' and photographic comparison will be used to assess decrease in size and number of warts and thus the response to treatment. The clinical improvement will be rated as complete response, excellent response, good response, poor or no response by the patient and physician global assessment using visual analog scale score at each visit taking baseline clinical photograph as controls. Immediate and late adverse effects of MMR vaccine and Vitamin D will be evaluated after each treatment session. Necessary investigations and intervention will be done if needed. Follow up will be made monthly for three months to detect any recurrence.

Quality of Life

Quality of life (QoL) will be measured in wart patients, using the Nepali version of the dermatology life quality index (DLQI) questionnaire before initiation of treatment and at the end of follow up. DLQI contains 10 questions that involves 6 sections: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Questions 1 and 2 assess symptoms and feelings; 3 and 4, daily activities; 5 and 6, leisure; 7, work and school; 8 and 9, personal relationships and 10, treatment.

The DLQI consists of 10 questions. Each question is given 4 options from not at all effect (score 0) to very much effect (score 3). The minimum and maximum possible score, thus, is 0 and 30 respectively. The interpretation of the patients' score is done as follows:

Meaning of DLQI Scores

0-1 = no effect at all on patient's life

2-5 = small effect on patient's life

6-10 = moderate effect on patient's life

11-20 = very large effect on patient's life

21-30 = extremely large effect on patient's life

The clinically meaningful change or reduction in the DLQI score is measured as the change in score from one band to the other in the above-mentioned interpretation chart.

Statistical analysis

1. **Data handling:** Data will be entered in Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA) and statistical analysis will be done using Statistical Package for the Social Sciences 10.5 version (Chicago, Inc)
2. **Coding:** Alpha numerical code will be used
3. **Monitoring:** Data will be entered after every day of work and supervised by guide.
4. **Statistical analysis** will be conducted as per both per-protocol and intention-to treat population (defined as all enrolled patients to whom study drug will be given; with the last observation carried forward) basis using two sided tests.

For *descriptive statistics*, percentage, mean, S.D., median, and minimum, maximum will be calculated along with graphical and tabular presentation.

For *inferential statistics*, statistical methods that will be used are as follow

- a. Chi square test and Fisher's exact test to compare the categorical data between the groups.
- b. Paired t test for comparing normally distributed continuous variables (pretreatment and post treatment DLQI) at different time point within the groups.
- c. Mann- Whitney U test to compare the not normally distributed variables (age, duration of illness, size, number)
- d. Kaplan–Meier curves to compare the response rate (complete, excellent, good or poor response) on each follow up visit (week 3, 6, 9, 12) between the groups.

Test of significance will be considered when value of $p \leq 0.05$.

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ANNEXURES

Department of Dermatology and Venereology

BPKIHS, Dharan

Proforma for Wart patients

SN: Group: OPD/Inpatient no: Date:

Name

Age (years): Sex:

Race/ethnicity:

Education: Occupation:

Address: Phone no.

History:

1) Duration of wart: 2) Type of wart:

3) Site of lesions: Scalp/Face/Neck/Trunk/Upper extremities/Lower
Extremities/Palms/soles/finger/toes

4) Number of Lesions at presentation:

5) Size of lesion:

6) Progression of lesion: Gradual/Rapid/Stable/ Regressing

7) Any associated Symptoms:

 Pruritus: none/ mild/ moderate/ severe

 Pain: none/ mild/ moderate/ severe

 Burning sensation: none/ mild/ moderate/ severe

8) Associated personal Systemic illness: Yes/No

If yes: HIV/ Diabetes/ Asthma/ Allergic skin disorders/ Convulsion/ bone pain/ muscle weakness

9) Pregnant/ lactating mother: Yes/No/ NA

10) Taking any other drugs: Yes/No

If yes: Corticosteroids/ Immunosuppressive/ Others

11) Past treatment taken: Yes/ No

 If yes: Self-care (Herbs/ Drugs/ Bought from pharmacy)

 Traditional (Traditional healer/ Herbalist/ Other)

 Seek medical help or treatment (Topical/ Systemic/ Both/ Surgical)

 Improvement: Worse/ No/ Mild/ Moderate/ Good

 Time since last treatment:

 Reason for treatment:

Treatment given: IL MMR/ IL Vitamin D

Response to treatment

Number of visits	Date	Percentage decrease from baseline	Percentage decrease from last visit	Side effects (pain ,redness, edema, Infection, scarring, ulcer, pigmentary changes, flu like symptoms, anaphylaxis, confusion, polyuria, polydipsia, anorexia, nausea, vomiting, muscle weakness, bone pain, altered sensorium)	Remarks (Vitamin D level 20 days after 3 rd visit, 1 month after last dose)
1 st					
2 nd					
3 rd					
4 th					
5 th					

Follow Up

Number of visits	Date	Percentage decrease from baseline	Recurrence (Yes/No)	Remarks
6 th				
7 th				
8 th				

छाला रोग जीवनस्तर मूल्याङ्कन प्रश्नावली

दर्ता नं.:

मिति:

डिएलक्यूआइस्कोर

नाम:

रोग:

ठेगाना:

यो प्रश्नावली को उद्देश्य गत हप्तामा छालाको समस्या ले गर्दा तपाईंको जीवनलाई के कतिको प्रभाव परेको छ भनि बुझ्ने हो । कृपया, प्रत्येक प्रश्नमा दिएका जवाफहरूमध्ये जुन उपयुक्त लाग्छ एउटा बाँक्समा चिन्ह लगाउनुहोस् ।

१.	गत हप्ता, तपाईंको छाला कतिको चिलाउने, पोल्ने दुख्ने, वा विभ्रते गरेको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
२.	गत हप्ता, तपाईंको छालाको समस्याले गर्दा कतिको लज्जत वा आफैलाई अष्टेरो परेको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
३.	गत हप्ता, तपाईंको छालाले गर्दा किनमेलमा जाँदा, घरायसी काम गर्दा वा बगेचा जाँदा कतिको अष्टयारो परेको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन <input type="checkbox"/>
४.	गत हप्ता, तपाईंको छालाले गर्दा आफ्नो पहिरनमा कतिको प्रभाव परेको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन <input type="checkbox"/>
५.	गत हप्ता, तपाईंको छालाले गर्दा सामाजिक वा अतिरिक्त क्रियाकलापमा कतिको असर परेको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन <input type="checkbox"/>
६.	गत हप्ता, तपाईंको छालाले गर्दा तपाईंलाई खेलकुद गर्न कतिको कठिनाई परेको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन <input type="checkbox"/>
७.	गत हप्ता, तपाईंको छालाको समस्याले गर्दा आफ्नो काम वा पढाईमा रोक लागेको थियो ?	थियो । थिएन ।	<input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन <input type="checkbox"/>
	यदि "थिएन" भने गत हप्ता तपाईंको काम अथवा पढाईमा कतिको समस्या आएको थियो ?	ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
८.	गत हप्ता, तपाईंको छालाको समस्याले गर्दा तपाईंको श्रीमान/श्रीमती, कुनैपनि नाजिकको साथी, अथवा नातेदारसग कतिको समस्या भएको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन <input type="checkbox"/>
९.	गत हप्ता, तपाईंको छालाको कारण यौनजन्य समस्या कतिको परेको थियो?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन <input type="checkbox"/>
१०.	गत हप्ता, तपाईंको छालाको उपचारमा कतिको समस्या भोग्नु परेको थियो जस्तै : घर फोहोर हुनु अथवा समय बढी लागेको थियो ?	धेरै थियो । ठिकै थियो । अलिफत थियो । पटकै थिएन ।	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	महत्त्व थिएन । <input type="checkbox"/>

कृपया प्रत्येक प्रश्नको उत्तर दिनु भयो, हेर्नु होला । धन्यवाद ।

Department of Dermatology and Venerology

BPKIHS, Dharan, Nepal

Patient Information Sheet

I Dr. Bibisha Baaniya, Junior Resident of Department of Dermatology and Venereology at B.P. Koirala Institute of Health sciences, am doing a research under supervision Of Chief Guide **Dr. Nidhi Shah**. The title of research is “**A comparative study to assess efficacy of Intralesional MMR (Measles, Mumps, Rubella) vaccine and Intralesional Vitamin D3 in treatment of Warts**”. I am going to give you information and invite you to be the part of this research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask me, the study doctor or the staff.

Importance of the research

Intralesional immunotherapy is a newly emerged but more comfortable, efficacious and cost effective method of treatment of warts.

Purpose of the research

1. To determine the efficacy of IL MMR vaccine in the treatment of Wart
2. To determine the efficacy of IL Vitamin D in the treatment of wart
3. To compare the efficacy of IL MMR vaccine and IL Vitamin D

Participant selection: We are inviting all the patients attending dermatology OPD diagnosed as Warts.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this hospital for treatment of your condition.

Procedures and Protocol

A preset proforma will be filled up for every patient which includes personal data, past history, medical history, drug history, clinical data like site, size, number, distribution. A thorough clinical examination of the patients will be recorded.

The session of injection will be done at 3 weekly intervals for a maximum of 5 sessions or until complete resolution of warts, whichever is earlier and thereafter monitoring will be done monthly for 3 months. Photograph of the lesions will be taken before the first treatment session, in every treatment session and 3 months after last session. In patients of group B who need 3 or more sessions, serum vitamin D level will be measured after 20 days of 3rd dose and 1 month after the last dose to ensure safe monitoring.

Direct or indirect benefits to participant, community or others

Compared to other destructive modalities, immunotherapy is more effective and comfortable for the patient as it obviates the need for individual treatment of each wart. In addition it has a lower rate of recurrence, avoids adverse effects such as scarring, is more cost-effective in multiple warts and decreases the time a physician has to spend on each patient. Further it can be easily made available in

periphery, hence the impact that it is going to have becomes multifold especially in context of Nepal.

Foreseeable Risks, discomfort or inconvenience to patient

Side effects include pain during injection, flu-like symptoms, pruritus, burning sensation, edema, mild erythema, hyperpigmentation.

Cost and source of investigations, drugs, and surgery

Patient must bear the cost of drugs. However, the cost of measuring serum vitamin D level and injecting procedure will be free of charge and we investigator ourselves will be liable for this. If any adverse effects occur then the consultation charge will be free but patient must bear the drug charges if needed. Insurance coverage will be provided as per Social Health Insurance scheme of Nepal government.

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except those working in the Department of Dermatology.

Sharing the Results

The knowledge that we get from doing this research will be published in a thesis paper and later may be published in a scientific research journal.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Whom to Contact

If you have any questions you may ask me now or later, even after the study has started. If you wish to ask questions later, you may contact:

Dr. Bibisha Baaniya

BPKIHS, Dharan

Email Address: cul.bibisha@gmail.com

Phone no: 9841744777

Department of Dermatology and venereology

BPKIHS, Dharan, Nepal

Informed consent

Name of the Candidate:

Age: Gender:

Address:

Telephone no. Email:

The content of the information sheet dated.....that was provided have been read carefully by me/explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have the opportunity to ask questions.

The nature and purpose of the study and its potential risks/benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or illegal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from BPKIHS. I give permission for these individuals to have access to my record.

I hereby give consent to take part in the above study and allow to perform the procedure and any other medical service that may become necessary during the procedure.

I also consent for medical photographs/video and I have been informed that these photographs/video will be used without revealing the identity. I understand that

these along with the information I provide may be used in medical record, for purpose of publication in textbook or medical journal and dissertation purpose, or for medical education.

The consent form has been signed by me when I was not under the influence of any drugs.

Patient's Signature.....

Researcher/ doctor's signature.....

Guardian's signature.....

Date:

Witness Signature:

If Illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions and to understand the nature of the study. I confirm that the individual has given the consent freely.

Researcher/Doctor's Signature.....

Date:

Witness signature.....

Thumb print of participant

Right

Left

