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Comparative study between intralesional MMR and intralesional BCG in treatment of verruca vulgaris

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Abstract: *Background: Cutaneous warts are common dermatological conditions caused by the human papilloma virus (HPV). Immunotherapy has now found a significant place in the treatment of warts because of its non-destructive action, ease of use, and promising results. Objectives:To compare efficacy between intalesional MMR and BCG in treatment of verruca vulgaris. Method: 30 Patients were included in study and divided into two groups. Group1:This group included 15 patients subjected to intralesional MMR. Group 2:This group included 15 patients subjected to intralesional BCG. Only single wart was injected at 2-weeks interval until complete clearance or for a maximum of 5 treatments. Follow up of patients was done every month for 3 months for clinical assessment of results and to show any recurrence. Results: In group1: 73.3% of patients showed complete lesional clearance and 46.6% showed distant lesional clearance . 6% showed erythema around lesion & 26.6% showed hyperpigmentation. In group 2:33.3% showed lesional clearance and 13.3% showed distant lesional clearance. 60% of patients showed lesional ulceration and 30% showed flu like symptom & 53.3% showed hyperpigmentation. There is statistically significant differance ($p<0.05$) between both groups where MMR showed higher efficacy than BCG. Conclusion:. We found that the treatment of common warts by intralesional MMR vaccine is effective, with good cure rates, and excellent safety profile compared to intralesional BCG.*

Keywords: *BCG, immunotherapy, intralesional, MMR, verruca*

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I. Introduction:

Warts are benign tumours caused by infection of keratinocytes with HPV which are epitheliotropic nonenveloped small double-stranded DNA viruses.[1] Warts appear in various forms include: verruca vulgaris, plane, plantar, myrmecia, coalesced mosaic, filiform or digitate and periungual warts.[2] Although the spontaneous resolution rate for warts is 65–78%, the cosmetic disfigurement, tendency to spread, and associated poor quality of life warrants quick intervention.[3] Various modalities of treatment include destructive and immunotherapeutic modalities, but no single treatment has yet been proven 100% effective. Because of the cumbersome nature of destructive procedures and a high risk of recurrence, immunotherapy is becoming more and more popular, especially in the treatment of refractory warts. 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. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in general.[4]

The exact mechanism of action of intralesional immunotherapy is still unclear. Proposed mechanisms include induction of a strong non‑specific inflammatory response against HPV infected cells. Antigen injection may be associated with proliferation of peripheral blood mononuclear cells that promote Th1 cytokine responses which include IL-2, INF-gamma and TNF-alpha. This further activate cytotoxic T cells and natural killer cells to eradicate HPV‑infected cells. This stimulated immune response could then subsequently destroy all lesions on the body, rather than the locally treated lesion.[5]

Autologous vaccine therapy is limited by the oncogenic potential of the virus. Therefore, a safe, inexpensive, effective and simple immunotheurapeutic agent is needed for the management of warts.[5] Agents used for immunotherapy of warts are Topical agents- Imiquimod, Sinecatechins, BCG and Intralesional (IL) agents- Mw vaccine, BCG vaccine, PPD, MMR vaccine, Candidial extract, Trichophyton antigen, Vitamin D3, Interferon alpha 2B and Systemic agents- Zinc, Cimetidine, Levamisole, HPV vaccines.[6] Current indications of immunotherapy include recalcitrant warts, recurrent warts, multiple warts and difficult to treat areas—periungual and palmoplantar sites.[4]

II. Aims & Objectives:

To study the efficacy of intralesional BCG vaccine & intralesional MMR vaccine individually & to compare the efficacy between both in the treatment of verruca vulgaris.

III. Materials & Methods

This is a hospital based comparative study done from February 2017 to July 2017 which included 30 patients who attended DVL department, Government General Hospital, Kakinada. All these patients gave informed consent to participate in this study

They were randomly assingned into two groups:

Group A: 15 patients subjected to 0.3 ml of intralesional MMR (into the largest verruca)

Group B: 15 patients subjected to 0.1ml of intralesional BCG (into the largest verruca)

3.1.Inclusion criteria

a. Patients with multiple verruca vulgaris (more than one)
b. Age more than 12 years
c. No concurrent treatment for verruca

3.2.Exclusion criteria:

a. Patients with fever or signs of any inflammation or infection
b. Children < 12 years
c. Pregnancy
d. Lactation
e. Immunosuppression
f. Anogenital/palmoplantar/planar warts
g. Patients who received any other treatments for verruca in the last month before enrollment
h. Past history of asthma, allergic skin disorders, meningitis or convulsions

Detailed history was taken from all patients. A thorough clinical examination for identification of the characteristics of the warts including site, size, number and presence or absence of distant warts. Photographs of the lesions at the first visit, then monthly for three months were taken. Only single largest wart was injected using an insulin syringe, at 2-weeks interval until complete clearance or for a maximum of 5 treatments. Follow up of patients was done every month for 3 months for clinical assessment of results and to show any recurrence.

The response was evaluated as complete clearance if there is disappearance of the verruca and appearance of normal skin, partial if there is 50-99% reduction in size and no response if the reduction is only 0-49% . Resolution of distant untreated warts was also assessed. The results obtained were statistically analyzed using SPSS/PC software.

IV. Results

Out of 30 patients, 17(56.6%) were males and 13(43.3%) were females with majority of patients were in the age group of 12-20yrs. Majority of patients were students -18(60%) , house wives -6(20%), manual labourers -3(10%), sedentary workers -3(10%). Family history was present in 9(30%) patients. Multiple verruca at same anatomical site was present in 18(60%) and involvement of other anatomic site was present in 12(40%). Out of 30 patients, 21(70%) patients had verrucae on dorsum of hands and forearms and 9(30%) had on dorsum of feet and legs.

On comparing the treatment responses at the lesional site at the end of 1month, we found no statistically significant difference between MMR & BCG group. 5(33.3%) MMR group showed complete clearance whereas 4(26.6%) BCG group showed complete clearance but as regard to partial clearance it was 6(40%) vs 4(26.6%) respectively and as regard to no response it was 4(26.6%) vs 7(46.6%) respectively.

On comparing the treatment responses at distant site at the end of 1month, there was significant difference in clearance rate where MMR showed higher efficacy compared to BCG group (complete clearance 3(20%) vs 1(6.66%) respectively, partial clearance 5(33.3%) vs 1(6.66%) respectively and no response 7(46.6%) vs 13(86.6%) respectively).

While at the end of 3rd month there was statistically significant difference both at lesional site and distant site where higher efficacy was seen with MMR compared to BCG - complete clearance 11(73.3%) vs 5(33.3%) respectively, partial clearance 3(20%) vs 4(26.7%) respectively and no response 1(6.7%) vs 6(40%) respectively at lesional site and at distant site complete clearance 7(46.6%) vs 2(13.3%) respectively, partial clearance 7(46.6%) vs 2(13.3%) respectively and no response 1(6.7%) vs 11(73.3%) respectively .

In MMR group, only one patient (6%) showed erythema around lesion and 4(26.6%) showed hyperpigmentation whereas in BCG group, 9 (60%) patients showed lesional ulceration 5 (30%) showed flu like symptoms and 8(53.3%) showed hyperpigmentation.

Table 1: Age characteristics of the patients

Age of patient	No. of patients (%)
12-20 years	14
21-30 years	9
31-40 years	7
Mean 21.96	
SD 6.79	

Table 2 : Sex distribution of patients

Gender of the patient	No. of patients (%)
Male	17(56.6%)
Female	13(43.3%)

Table 3: Occupation distribution of patients

Occupation of the patient	No. of patients (%)
Students	18(60%)
House wives	6(20%)
Manual labourers	3(10%)
Sedentary workers	3(10%)

Table 4: Distribution of lesions

Site of involvement	No. of patients (%)
Dorsum of hands and forearm	21(70%)
Dorsum of feet and legs	9(30%)

Table 5: Side effects of MMR group

Side effects	No. of patients (%)
Erythema	1(6%)
Hyperpigmentation	4(26.6%)

Table 6: Side effects of BCG group

Side effects	No. of patients (%)
Lesional ulceration	9(60%)
Flu like symptoms	5(30%)
Hyperpigmentation	8(53.3%)

Table 7: comparision of response rates at the end of 1 month between two groups

	MMR group	BCG group	P value
	Lesional site		
Complete clearance	5 (33.3%)	4 (26.6%)	
Partial clearance	6 (40%)	4 (26.6%)	
No response	4 (26.6%)	7 (46.6%)	p>0.05
	Distant site		

Complete clearance	3 (20%)	1 (6.66%)	P<0.05
Partial clearance	5 (33.3%)	1 (6.66%)	
No response	7 (46.6%)	13 (86.6%)	

Table 8: Comparison of response rates at the end of 3rd month between two groups

	MMR group	BCG group	P value
	Lesional site		
Complete clearance	11 (73.3%)	5 (33.3%)	
Partial clearance	3 (20%)	4 (26.7%)	
No response	1 (6.7%)	6 (40%)	P<0.05
	Distant site		
Complete clearance	7 (46.6%)	2 (13.3%)	
Partial clearance	7 (46.6%)	2 (13.3%)	
No response	1 (6.7%)	11 (73.3%)	P<0.05

Figure 1: Bar diagram showing response rate at the end of 1month at lesional site

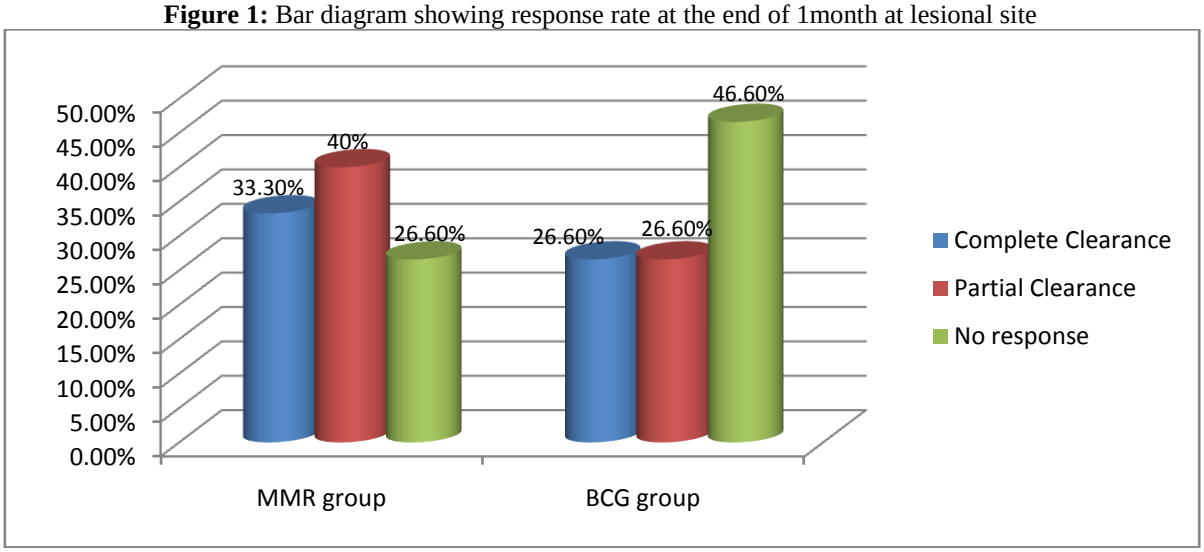


Figure 2: Bar diagram showing response rate at the end of 3rd month at distant site

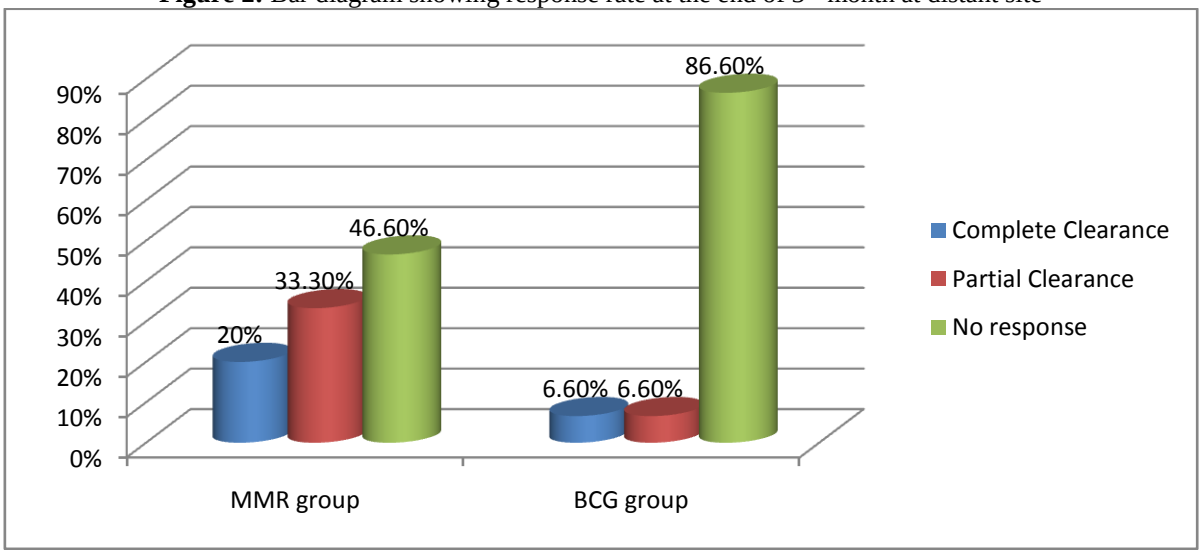


Figure 3 Bar diagram showing response rates at the end of 3rd month at lesional site

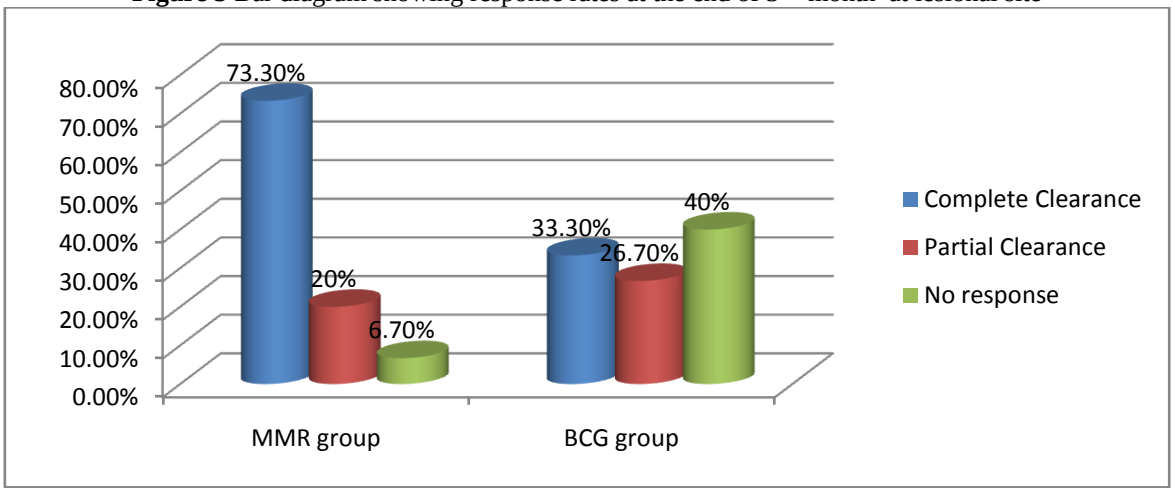
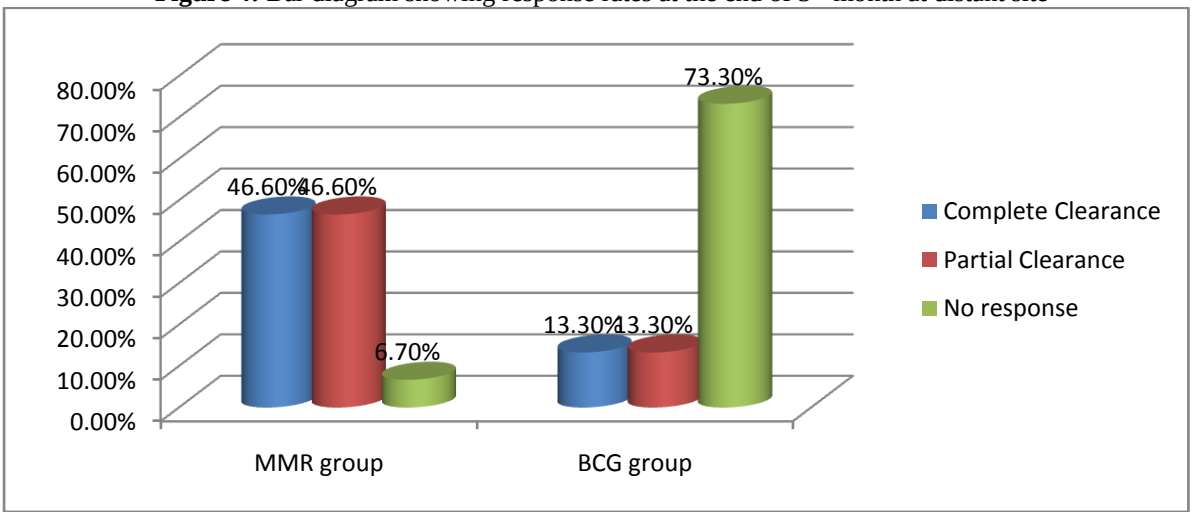


Figure 4: Bar diagram showing response rates at the end of 3rd month at distant site



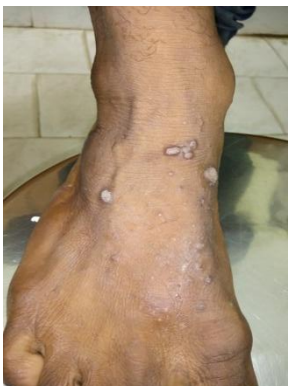


Figure 5 Verruca before treatment

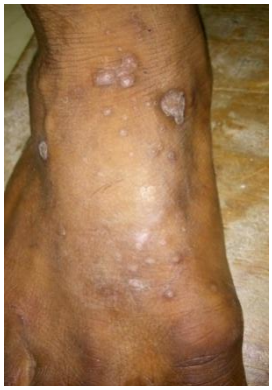


Figure 6 Verruca 1 month after intralesional MMR

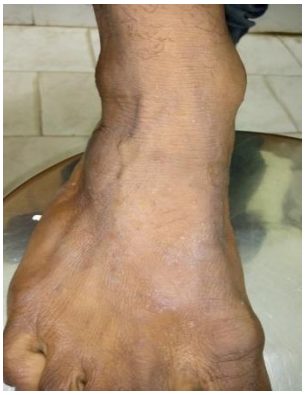


Figure 7 Verruca at the end of 3rd month of treatment

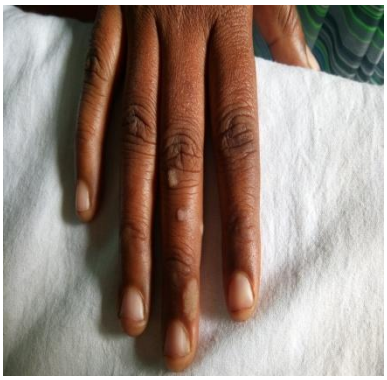


Figure 8 Verruca before treatment

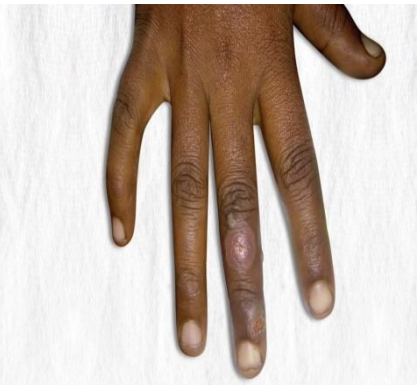


Figure 9 Verruca at the end of 1st month after intralesional BCG

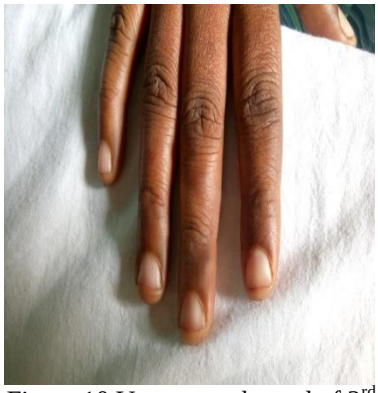


Figure 10 Verruca at the end of 3rd month of treatment

V. Discussion

Although most of the therapeutic options result in clearing of virus within 1-6 months, in 20-30% of the patients, relapses and new lesions will appear as a result of failure of the cellular immune system to detect and remove the lesions. There are clinical evidences that cellular immune responses play an important role in HPV infection and disease.[7] Immune mechanisms have been suggested to explain the spontaneous resolution of warts. If this immunity could be enhanced, wart resolution could be long lasting. The stimulated immune system would destroy all warts in the body, saving the patients the local treatment for each individual wart. It has been reported that untreated warts resolve after injection of only one wart with intralesional immunotherapy that induces HPV-directed immunity.[8] This is a unique advantage of intralesional immunotherapy over conventional treatment modalities as with later, only the lesions treated are cleared whereas with former ones distant lesions which are not treated also cleared.[9]

In some of the previous studies, it has been shown that mumps-measles-rubella (MMR) vaccine results in regression of warts via immunomodulation and induction of immune system. This method can be used in larger populations because of vaccine availability and safety.[7] BCG vaccine is another addition to growing list of antigens suitable for intralesional immunotherapy. BCG vaccine, being easily and widely available, appears to be a promising armamentarium in the treatment of refractory warts.[9]

We aimed in this work to evaluate the effectiveness two variants of immunotherapy that is intralesional MMR and intralesional BCG and also to compare between them in treatment of common warts.

The demographic characteristics such as age, sex, site of warts are comparable in both the groups. Majority of patients in present study were between 12-20 yrs with mean age of 21.96 ± 6.79 years. Males out numbered females probably due to their outdoor working condition. Dorsum of hands and feet were the common sites involved probably due to more exposure and susceptible for trauma, pricks, and inoculation. There was no statistically significant difference in response to treatment in terms of age, sex, number, duration and site of warts in both the groups.

In our short study MMR group showed complete remission in 11(73.3%), partial response in 3(20%) and no response in 1(6.7%) at lesional site at the end of 3rd month, these results were in concordance with Nofal et al., study which showed complete response in 57 patients (81.4%), partial response in seven patients (10%), and no response in six patients (8.6%)[10], Dhope et al., (n=20) showed complete response in 13(65%), partial response in 4(20%) and no response in 3(15%) patients [11], Saini P et al., study (n=86) showed 46.9% complete response and 20.9% partial response[12], Raju et al., study (n=27) showed complete remission in 19 patients (70.4%), partial remission in 6 patients (22.2%) and no remission in 2 patients (7.4%)[13], Naseem et al., (n=150) showed complete response in 81%, partial response in 10% and no response in 9%[2].

While comparing results at distant site with MMR group our study showed complete response in 7(46.7%) partial response 7(46.7%) in and no response in 1(6.7%) which is in discordance with Mohamed et al., study. This study showed complete response in 22(86.9%) and partial response in 3(13.1%).

In our study BCG group showed complete remission in 5(33.3%), partial response in 4(26.7%) and no response in 6(40%) at lesional site at the end of 3rd month, these results were in concordance with Kenawi et al., study (n=30) which showed 40% complete remission, 40% partial remission and 20% no response[14], and Sharquie e al., study showed 39.7% complete remission and 59.5% no response[15].

In Dhope et al., study (n=20) MMR group showed pain in 85% patients and erythema, swelling, and flu‑like symptoms in almost some numbers of patients, i.e., 25%, 20%, and 10%, respectively[11] where as in our study MMR group showed erythema 1(6%) and hyperpigmentation in 4(26.6%).

In Kenawi et al., study (n=30) BCG group showed flu like symptoms in all patients and lesional ulceration in 26.7% with necrosis in 16.7%[14] where as our study showed flu like symptoms in 30%, lesional ulceration in 60% and hyperpigmentation in 53.3%

VI. Conclusion

Intralesional MMR has a better efficacy over intralesional BCG both in lesional and distant clearance of warts. Intralesional BCG was associated with more side effects (lesional ulceration and flu like symptoms) while no significant side effects were observed with intralesional MMR. Hence, to conclude intralesional MMR is safer, better and effective treatment modality of multiple verruca vulgaris compared to BCG.

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