

Original Research Article

Therapeutic evaluation of efficacy of intralesional bleomycin in common warts including palmo-plantar and periungual warts: a prospective study

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ABSTRACT

Background: Commonly used destructive treatment modalities for common warts though effective, are associated with pigmentary changes, scarring and recurrences. Treatment with immune modulators or immunotherapy has shown variable results. We evaluated efficacy and safety of intralesional bleomycin for treating common warts including palmoplantar and periungual warts.

Methods: Two hundred patients with common, palmar, plantar and periungual warts (having 753 warts) were treated with two intralesional injections of bleomycin 1 mg/ml at two weekly intervals. They were followed up at 4 weeks and 12 weeks for cure, adverse effects and partial clearance or recurrence.

Results: Only 183 (M: F 95:88) patients having 703 warts completed the study. Overall, complete clearance in 669 (95.16%) warts in 156 (85.2%) patients and partial clearance in 24 (3.4%) warts in 21 (11.4%) patients were observed. Patients with complete/partial clearance were highly satisfied from the treatment. Recurrence was seen in 6 (3.27%) patients. Most patients had injection site pain for 2-3 days not warranting discontinuation of treatment. Other adverse effects included temporary hyperpigmentation in 46, altered skin texture in 12 and injection site infection in 6 patients, respectively.

Conclusions: Intralesional bleomycin appears effective, safe, and acceptable treatment modality for common warts including palmoplantar and periungual warts. It carries the advantage of low dose, insignificant adverse effects and high patient satisfaction.

Keywords: Warts, Bleomycin, Intralesional, Immunotherapy

INTRODUCTION

Warts are caused by human papilloma virus (HPV) infection of fully differentiated epithelium of skin and mucous membranes. The subsequent proliferation of virus infected cells results in clinically evident polymorphic warty papules or plaques. Over 100 HPV types have been recognized having an affinity for different body sites. The prevalence of cutaneous warts is high in children aged between 12 and 16 years followed

by a significant decline after the age of 20 years. Warts typically continue to increase in size and distribution and may become more resistant to treatment over time. Children with treatment resistant warts may be the potential reservoirs for HPV transmission.¹ Since most warts in immunocompetent individuals are self limiting and resolve spontaneously within months or years, a policy of no treatment is often advocated. However, plantar and periungual warts can be painful and warts on cosmetically important areas such as face and hands may

affect patient's quality of life.² The most common indications for the treatment of cutaneous warts include pain, functional impairment, cosmetic reasons, and the risk of malignancy.³⁻⁶ There is no single treatment option that has been proved 100% effective and hence many treatment modalities exist with variable cure rates. The intralesional injection of anti-neoplastic drug bleomycin appears promising treatment for common warts in view of its properties of preferential binding in squamous cells, DNA strand scission and limited toxicity. Intralesional bleomycin has been used for treatment of warts with excellent results. Therefore, this study was conducted to evaluate efficacy and safety of intralesional bleomycin for treatment of common warts including palmoplantar and periungual warts.

METHODS

The study was conducted at Dr Rajendra Prasad Government Medical College and hospital, Kangra at Tanda (Himachal Pradesh, India) after obtaining clearance from institutional ethical committee and registration with clinical trial registry from April 2017 to March 2018. Two hundred consecutive patients having common warts over dorsal hands, feet, palms, soles and periungual skin were enrolled irrespective of number and duration of warts or previous treatments. Pregnant and lactating women, children ≤ 12 years, patients with apparent skin infection, abnormal hepatorenal functions, Raynaud's phenomenon, peripheral vascular disease or immunosuppression were excluded.

Clinical details regarding age, gender, duration of warts and previous treatments were recorded. The patients were subjected to laboratory tests for complete blood counts, liver function tests, and renal function tests before and after end of the study period of 12 weeks of treatment. The location, number, size and clinical type of each wart selected for treatment was recorded.

Procedure

Bleomycin is available in vials containing 15 mg powder. It was diluted first with 5 ml distilled water to prepare a 3mg/ml stock solution that can be stored for 60 days at 4°–8°C. Two parts of 2% lignocaine and one part of the bleomycin stock solution was taken in a 30G needle insulin syringe to obtain a final concentration of 1 mg/ml. Each wart and the adjacent skin were cleansed with spirit and bleomycin (1 mg/ml) was injected intralesionally using insulin syringe till complete blanching of the lesion but total dose did not exceed 2 mg per session. The maximum volume of bleomycin injected for small warts was 0.1 ml and did not exceed 0.2 to 0.3 ml for larger warts injected at various points of a lesion. The treated lesions were covered with sterile dressing at end of the procedure. Patients were given oral diclofenac (50 mg twice daily) for post injection, swelling, and pain during first 2-3 days and prophylactic antibiotics (co-amoxiclav 625 mg given orally twice daily for five days). The

patients were asked to return immediately in case they experience any unusual pain and for follow up at 2 weeks for paring of eschar and residual wart or repeat treatment. The residual warts if present were treated with repeat intralesional bleomycin in a similar fashion. Patients were then followed up till 12 weeks for any adverse effects and resolution or recurrence of warts without further treatment.

Evaluation for therapeutic outcome

Clinical photographs were taken at baseline, and follow-up visits at 2 weeks, 4 weeks and 12 weeks for pretreatment and post treatment comparison. They were advised to report any time in case of recurrence. The clinical response was graded as shown in Table 1. At each visit, occurrence of systemic or local adverse reactions such as pain during and after treatment, pigmentary changes, Raynaud's phenomenon, scarring, tissue/nail damage, itching and skin rash, and their severity, if any were noted. Patient satisfaction score was assessed based on five point Likert scale at end of 12 weeks study period (Table 1).

Table 1: Grades of improvement and Likert scale for patient satisfaction score.

Grades	Definition
Complete clearance	Complete disappearance of warts and skin texture at the site is restored to normal
Partial clearance	Residual wart still visible
No change	No change in size and texture
Recurrence	Recurrence during the study period
Likert scale for patient satisfaction score	
Satisfaction level	Score
Very much satisfied	5
Somewhat satisfied	4
Undecided	3
Not really satisfied	2
Not at all satisfied	1

Statistical analysis

MS Word Excel software was used to tabulate and analyze the data. The continuous data are presented as means \pm standard deviation (SD) and categorical variables are presented as frequencies and percentages. Mann-Whitney non-parametric test was used for variables that were not distributed normally.

RESULTS

Table 2 depicts baseline characteristics of study patients. Out of 200 patients 183 completed the study and comprising 95 men and 88 women (M: F=1.07:1) aged between 13 and 81 (mean \pm SD 27.59 \pm 12.57) years.

Seventeen patients did not complete the study. Eleven patients were lost to follow up after the first dose and six patients did not turn up after second dose. The duration of warts was 1 month to 15 years (Mean±SD 16.5±30.26 months) and 136 (74.31%) patients had them for less than one year. The number of warts varied between 1-22

(Mean 3.85) and the majority, 117 (63.93%) patients had <5 warts. Sixty six (36.06%) patients had received treatment in the past with topical salicylic acid 20% (corn cap), electrocautery, cryotherapy, intralysional MMR immunotherapy, and indigenous treatments, alone or in combination, for variable periods without benefit.

Table 2: Baseline profile of patients (n=183).

Baseline characteristics		Number of patients (%)
Gender	Males	95 (51.91)
	Females	88 (48.08)
	M:F	1.07:1
Age in years	Range	13-81
	Mean ±SD	27.59±12.57
	13-20	58 (31.7)
	21-40	100 (54.64)
	41-60	19 (10.38)
	>60	6 (3.27)
Duration of warts	Range	1 month-15 years
	Mean±SD (months)	16.5±30.26
	<6 months	79 (43.16)
	6 months-1year	57 (31.14)
	>1 years	39 (21.31)
	>10	8 (4.3)
Number of warts	Range	1-22
	Mean	3.85
	<5	117 (63.93)
	5-10	37 (20.21)
	>10	29 (15.84)

Table 3: Clearance of warts at each visits and cure rate at end of 12 weeks study period (n=703).

Sites and size of warts	Number of warts	After first dose (%)	After second dose (%)	At 12 weeks (%)	Complete clearance (%)	Partial	Recurrence
Sites*	Number of warts (%)						
Plantar	296	29	242	10	281 (94.9)	11	4
Dorsal hands and feet	237	44	156	29	229 (96.62)	7	1
Palmar	103	33	52	11	96 (93.2)	3	4
Peri-ungual skin	67	17	34	12	63 (94.2)	3	1
Total	703	123 (17.49)	484 (68.84)	62 (8.8)	669 (95.16)	24 (3.4)	10 (1.42)
Size	Number of warts (%)						
<10 mm	605	104 (17.2)	438 (72.39)	43 (7.1)	585 (96.7)	17 (2.8)	3 (0.5)
10-20 mm	91	19 (20.9)	46 (50.5)	12 (13.2)	77 (84.61)	7 (7.7)	7 (7.7)
>20 mm	7	0	1 (14.3)	3 (42.8)	4 (57.14)	1 (14.3)	2 (28.57)

*Includes patients having multiple sites involved

Table 3 depicts distribution and size of warts. Overall, there were 703 warts in 183 patients and included 296 (42.1%) plantar warts, 103 (14.6%) palmar warts, and 67 (9.53%) periungual warts. Two hundred thirty seven (33.71%) warts were present over dorsal hands and feet. Seven (1.05%) warts had mosaic morphology. The majority, 605 (86.05%) warts measured less than 10 mm

in size while 91 (12.94%) warts were between 10 and 20 mm in size.

Tables 3 and 4 show clearance of warts at every visit. Overall 156 (85.24%) patients were cleared of 669 (95.1%) warts at the end of 12 weeks study period. Complete clearance of warts was observed after first session itself in 123 (17.49%) warts in 63 (34.4%)

patients and they were taken off from further treatment. The 484 (68.84%) warts in 76 (41.53%) patients showing partial response after first dose resolved completely after second treatment session and no further treatment was given. Remaining 62 (8.81%) warts in 17 (9.28%) patients cleared at the end of 12th week. A complete or

partial response was observed in all warts treated with intralesional bleomycin. Only 24 (13.11%) warts showed partial clearance and 10 (1.42%) warts showed recurrence at the end of 12-week study period. Six patients who had received one dose of bleomycin showed recurrence at end of 12-week study period.

Table 4: Response to treatment at different visits (n=183).

Number of dose and follow up visits	Response to treatment	Number of patients (%)
First dose	Complete clearance	63 (34.4)
	Partial clearance	120 (65.57)
Second dose	Complete clearance	76(41.53)
	Partial clearance	44 (24.4)
At the end of treatment	Complete clearance	17 (9.28)
	Partial clearance	21 (13.11)
Total	Complete clearance	156 (85.24)
	Partial clearance	21(11.4)
	Recurrence	6(3.27)

Table 5: Therapeutic outcome following different techniques of bleomycin administration.

Modality used	Bleomycin dose and treatment schedule	Cure rate (%)	Remarks
Dermojet ⁹	1-3 ml bleomycin (1.0 mg/ml)	89.9	Included recalcitrant palmoplantar warts
Prick method with Monolet needle ¹⁰	1 mg/mL repeated monthly until warts cleared	92	Included palmoplantar and periungual warts
Multiple puncture technique with bifurcated needle ¹¹	1.0 mg/ml	92	Included periungual and genital warts
Translesional multipuncture Technique ¹²	0.1 mg/ml	74	Included periungual warts
Dermatography ¹³	0.1-1.0 mg/ml	63	Included resistant warts
Combination of Pulsed dye laser and intralesional bleomycin ¹⁴	Laser 7 mm spot, fluence 10 J/cm ² , + Bleomycin 0.5 mg/ml	89	Resistant warts. Immunosuppressed patients were also included
Bleomycin-impregnated tape ¹⁵	60 µg/cm ² tape, applied QD	69	Common warts, no response seen in plantar warts
Bleomycin microneedle patch ¹⁶	Micro needle patch containing 15% bleomycin	61.9	Common warts including plantar warts

Most common adverse effect observed was injection site erythema, induration and pain requiring treatment with oral diclofenac (50 mg, twice daily for 3-5 days). It lasted for 2-3 days only in few patients. Hyper-pigmentation that resolved over time in 46, skin texture changes in 12, and injection site secondary infections in 6 patients, respectively were other adverse effects noted. However, these did not warrant discontinuation of treatment. No nail dystrophy or other adverse effect on nail plate was seen following periungual bleomycin injection. None of patient had any haematological or biochemical abnormality after completion of treatment. No other systemic adverse effects occurred in any patient. All cured patients were very satisfied (overall satisfaction score 5 on Likert scale) with the therapeutic outcome.

DISCUSSION

Although children between 12 and 16 years of age are affected more frequently, warts are self limiting in them and most studies do not include children accounting for their less number in reported literature. As was also observed in this study, warts typically occur over dorsal hands, feet, palms and soles, and without treatment may continue to increase in size and distribution. However, they are usually asymptomatic and rarely require treatment. Nevertheless, plantar and periungual warts can be painful and warts on cosmetically important areas such as face and hands may affect patient's quality of life.

Moreover, they may become resistant to treatment over time and be a source of infection to others. Cosmetic disfigurement, pain, functional impairment and risk of malignancy are common indications for their treatment. A number of treatment options including immunotherapy, medical, surgical or other destructive procedures and have been proven not to be hundred percent effective and bereft of adverse effects such as post procedure scarring.⁷ We also made similar observations in our 66 patients who had received many treatments such as salicylic acid 20% (corn plaster), electrocautery, cryotherapy, intralesional MMR vaccine immunotherapy, and many indigenous treatments without benefit and frequent relapses. Although yet to be approved by USFDA, intralesional bleomycin using various techniques and concentrations has been used to treat common warts over hands, feet and periungual skin with good results and cure rates as high as 97% in several studies (Tables 5 and 6). Concentrations of bleomycin varying between 0.15% and 0.05% have been used for treating warts.⁸ Soni et al used intralesional bleomycin (1 mg/ml) to treat 85 palmo-plantar and periungual warts with high efficacy.²⁶ They observed complete resolution of 82 (96.5%) warts after one or two intralesional injections of bleomycin within 12 weeks. The response in palmo-plantar warts was 96% and it was 100% in periungual warts. Aziz-Jalali et al also reported complete remission in 95 (73%) and partial remission in 31 (24%) warts after intralesional bleomycin.²⁷ However, a high recurrence was observed in patients with more number of warts. We found this treatment modality significantly effective with overall complete cure rates in 85.24% patients having palmoplantar and periungual warts (Figures 1-4), while only 11.4% patients had partial cure at end of the 12-week study period. Whereas, cure rates for warts including palmoplantar and periungual warts was 95.16% as 669 warts showed complete resolution. Comparably, Salk and Douglas reported cure rate of 87% with a need of more than two treatment sessions with intralesional bleomycin in 13% of patients.²⁴ On the other hand, a cure rate of 63% was reported by Bremner while treating 142

warts in 24 patients.³⁴ The cure rate for periungual warts was 94.2% of 67 warts in our 35 patients with one or two injections of intralesional bleomycin. In a similar study it was 85.7% at 6 months comprising 15 patients with periungual warts treated with one or two treatment sessions of bleomycin sulfate using translesional multipuncture injections.¹² In general, cure rates with intralesional bleomycin (1 mg/ml) by other techniques such as dermojet was 77.5%, while it was 92% with monolet and bifurcated needle prick method in two separate studies.⁹⁻¹¹ This variability is perhaps due to inadequate bleomycin infiltration and incomplete coverage of large warts with monolet/bifurcated needle or dermojet techniques as some amount of the drug remains over wart surface with resultant wastage. For proper bleomycin injection drug should be delivered directly into wart, which is indicated by blanching of lesion. Too superficial injection may cause leakage of drug through warts. Deeper injection does not blanch. Multiple punctures in a larger wart may cause leakage of the drug and inferior therapeutic outcome. To prevent this, multiple punctures should be avoided and needle should be manipulated within the wart without withdrawing to deliver drug at the other end. Injections in periungual warts should be given with caution to avoid any damage to matrix as it may cause nail deformities, although this was not seen in any of our patients. Glasses should be worn at the time of injection as the drug may spray out following pressure and also patient should close his/her eyes. However other than technique of lesion infiltration, the dose of intralesional bleomycin could be another factor that may influence therapeutic outcome as has been observed by Hayes and O'Keefe.¹⁹ They obtained a cure rate of 73.3%, 87.5% and 90% by intralesional bleomycin in concentration of 0.25 mg/ml, 0.5 mg/ml and 1 mg/ml respectively. We observed 96.7% cure rate for lesions sized <10 mm compared to 82.6% in lesions sized >10 mm indicating that the size of the wart before the treatment is an important factor in predicting therapeutic response rather than their location, duration, number, or dose or technique for bleomycin infiltration used.

Table 6: Cure rate for warts with intralesional bleomycin.

Reference	Dosage and schedule for intralesional bleomycin	Cure rates (%)	Remarks
Bunney et al ¹⁷	0.5 mg/ml at 0, 3, 6 weeks and assessed at 12 weeks	76	Included treatment resistant warts.
		66	In extended parallel study.
Shumer and O'Keefe ¹⁸	1 mg/ml 2 weeks apart and followed up to 12 months	60	Warts of periungual and other skin areas responded better than plantar warts
Hayes and O'Keefe ¹⁹	1 mg/ml at 0, 3, 6 weeks final assessment at 3months	76	Included periungual and plantar warts
Amer et al ²⁰	0.1 ml for <5 mm and 0.2 for >5 mm of 1 mg/ml bleomycin, 2 injections 2 weeks apart for 8 weeks	47.6	Plantar warts
Sollitto et al ²¹	Original study could not be retrieved	32.2	Plantar warts

Continued.

Reference	Dosage and schedule for intralesional bleomycin	Cure rates (%)	Remarks
Golchai et al ²²	1 mg/ml injections 2 weeks apart for up to 3 injections	88.4	Included resistant palmoplantar and periungual warts
Sollitto et al ²³	1 mg/ml at 0, 1 week, 1 month and followed up to 6 months	65.4	Mosaic plantar warts
Salk and Douglas ²⁴	1.5 mg/ml 2 weeks apart and followed up to 6 months	87	Plantar warts
Dhar ²⁵	1 mg/ml 3 weeks apart for maximum 4 injections	97	Efficacy of IL bleomycin and cryotherapy was compared
Soni et al ²⁶	Two injections 2 weeks apart in 1 mg/ml strength. Followed up to 1 year	96.5	Included palmoplantar and periungual warts
Aziz-Jalali et al ⁷	1 mg/ml 4 weeks apart for maximum of 3 doses and followed up for 6 months	73	Included periungual warts
Kruter et al ²⁸	3 mg/ml 3 weeks apart. Followed up to 6 months	74	Warts over hands and feet including planter warts
Al-Naggar et al ²⁹	1mg/ml 2 weeks apart for maximum of 4 injections	70	Study compares I/L bleomycin vs microneedling-assisted topical bleomycin spraying for plantar warts
Barkat et al ³⁰	1mg/ml 2 weeks apart for maximum of 4 injections	69.3	Plantar warts
Unni and Tapare ³¹	1 mg/ml 2 injections 2 weeks apart and followed up to six months	93.1	Common warts
Mehta et al ³²	1 mg/ml 2 injections 2 weeks apart and followed up for 6 months	84	Common warts including periungual warts



Figure 1: (A) Multiple periungual warts over right index, middle and ring fingers; (2) two weeks after first bleomycin treatment after paring of eschar; (C) they cleared after one session of intralesional bleomycin without significant alteration of skin or nail texture; (D) complete clearance of all warts at 12 weeks. The deformity of middle finger is due to childhood injury.



Figure 2: (A) Multiple warts over dorsal hands and fingers; (B) Eschar formation two weeks after first bleomycin injection as seen before paring; (C) partial clearance of warts at 2 weeks after second treatment session; (D) complete clearance of warts at 12 week and two sessions of intralesional bleomycin. The mild hyperpigmentation over right hand was temporary and normalized during follow up period.

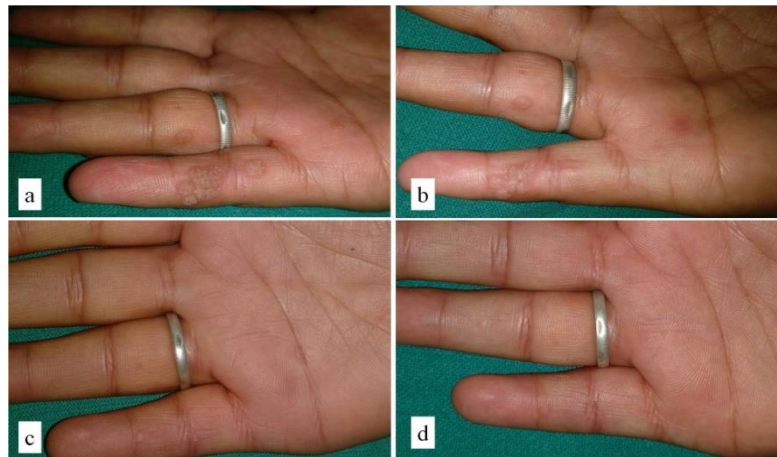


Figure 3: (A) Multiple palmar warts before treatment; (B) partial clearance at 2 weeks after one treatment session; (C) near total clearance of warts at 2 weeks after second treatment session; (D) complete clearance of warts two treatment sessions as seen at 12 weeks.



Figure 4: (A) Multiple plantar warts; (B) the black dry keratotic eschar formed two weeks after first bleomycin treatment session; (C) immediately after paring of eschar. No second dose was given; (D and E) near complete clearance of warts which cleared completely by 12 weeks.

The efficacy of intralesional bleomycin in warts has been found superior to placebo, cryotherapy and pulsed dye laser, etc. Shumer and O'Keefe in a placebo controlled double blind study found intralesional bleomycin superior in efficacy with cure rates of 60% for plantar warts and 94% for periungual warts.¹⁸ A significantly less number of treatment sessions for bleomycin treatment than cryotherapy were needed in a comparative study wherein clearance rate for warts was 97% and 87.6% for intralesional bleomycin therapy versus 82% and 72.3% for cryotherapy in two separate studies.^{25,33} The intralesional bleomycin was also highly effective in our 66 patients treated earlier with different modalities without benefit reflecting its superiority. All cured patients were very satisfied (overall satisfaction score 5 on Likert scale) with the therapeutic outcome.

Partial clearance in 24 (13.11%) warts and recurrence in 10 (1.42%) warts at the end of 12-week study period was perhaps from use of bleomycin in a suboptimal dose or inadequate infiltration of lesions. However, it is possible that some of the bleomycin treated warts may also show late clearance after 12 weeks as reported earlier by Bunney et al.¹⁷ They observed no response at 12 weeks in one of their case with large wart over knuckles that cleared after another 3 months without further treatment suggesting local persistence of drug even after discontinuation.

Common adverse effects observed were injection site erythema, induration and pain in all patients not warranting discontinuation of treatment. Immediate injection site pain was ameliorated with combining bleomycin with 2% lignocaine and oral diclofenac and co-amoxiclav in recommended doses in post treatment period was sufficient for symptomatic relief. Mild hyperpigmentation and textural skin changes in 46 and 12 patients, respectively, were temporary and normalized over a time. None of the patient showed adverse effect on nail unit following periungual bleomycin injection or any alteration of baseline haematological and biochemistry parameters. Intralesional bleomycin appears safe and effective treatment option in warts without causing systemic adverse effects.

Intralesional bleomycin appears an effective and safe treatment option for common warts including palmo-plantar and periungual warts with high patient satisfaction. It has advantages of using bleomycin in a dose less than usual systemic dose (30 mg twice weekly), and no significant systemic adverse effects. The intralesional injection does not require special puncture needles or technical expertise and there is minimal drug wastage from spills. While undertreated warts may recur, pre-treatment size of wart and adequate infiltration of lesions appear important factor for therapeutic efficacy. However, future studies may resolve issues related to regimen and dosage of bleomycin to treat all varieties of warts irrespective of their size, location, duration or previous therapies.

CONCLUSION

The study shows that intralesional bleomycin is an effective and safe option to treat common warts including palmo-plantar and periungual warts with high patient satisfaction. It has advantages of using bleomycin in a dose less than usual systemic dose (30 mg twice weekly), and no significant systemic adverse effects. The intralesional injection does not require special puncture needles or technical expertise and there is minimal drug wastage from spills. The pre-treatment size of wart and adequate infiltration of lesions appear important factor for therapeutic efficacy.

Limitations

Cross-sectional study design, small number of patients, lack of control group and short follow up are main limitations of this study. Different bleomycin concentrations were not compared and the efficacy and safety of intralesional bleomycin was not assessed in children.

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Ethical approval: The study was approved by the institutional ethics committee

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