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Neonatal Vaccination against Smallpox by Intradermal Route : A Clinical Assessment

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Intradermal vaccination of newborns within 24 h of birth was successful in 91·9% of the study population of 99 neonates against smallpox. The evolution of the vaccinial lesion and its progressive transition from one stage to another was comparatively quicker than is ordinarily experienced and simulated the previous description of **Accelerated Reaction** in revaccination. The results have been discussed with particular emphasis on freedom from post vaccinial complication, the possible role of passively acquired antibody on neonatal vaccination, the technical advantage of the method over the procedure usually employed, on viral implantation and replication. The technique, however, has a limited practical value in the field for routine primary and revaccination, but can be employed with great measure of success in institutions.

Introduction

Immunization of the newborns offers considerable advantages particularly in places where majority of the births are institutionwise, i.e. in hospitals and clinics. The newborns in such institutions are under constant medical supervision. Any complications resulting from vaccination are likely to receive immediate attention and treatment. The mothers worry and discomfiture are minimised as the babies would normally be under nursery supervision. The systematic reactions which accompany primary vaccination are also considered minimum at this period (WHO 1968). It is generally believed that such substantial advantages have little pragmatic value, mainly because the newborns may be refractory to primary vaccination, as they acquire high content of protective antibody across the placenta.

Material and Methods

Population vaccinated : Ninety-nine newborns at the Eden Hospital, Calcutta Medical College, during the period September to December 1968 were the subjects of vaccination. The average weight of the newborns was 2·7 kg. The mothers were mostly primigravida and were revaccinated at variable period in relation to this pregnancy. The scar following the primary vaccination was noted in each individual to confirm the history of primary vaccination. No definite confirmation was available regarding the revaccination and history as could be collected was the principal criteria in

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recording the revaccination status, therefore may not reflect the true nature of the revaccination position. Based on such informations the mothers were divided into five different groups, A, B, C, D, and E (Table I). Unless contraindicated the newborns were vaccinated within 24 h after birth. The follow up study was conducted under technically limiting conditions. The majority of the babies left the hospital on the fifth day and only 34 of the total vaccinated population of 99 stayed under observation till the seventh day and this handicapped a better evaluation of the evolutionary stages of the primary vaccination.

Vaccine lot used : Glycerinated calf lymph, Batch No. 3, 1968 manufactured locally by Vaccine Institute, Calcutta Corporation was stored in small aliquots at —20°C, was used in the study. The infectivity titre of the vaccine was 3×10^7/ml, as was estimated on chorio-allantoic membrane of 12-day old chick embryo and the bacterial content was within permissible limit (WHO 1965). The infectivity titre of the vaccine was determined again on completion of the study and no drop was observed. Each day an aliquot of the vaccine was taken out, diluted in equal volume of sterile phosphate buffered saline (pH 7·2) before use.

Table I. The measurement of the vaccinal lesion datewise

Days after vaccination	Average diameter of erythema in mm	Average diameter of lesion/ induration in mm	Std Deviation / Std Error† Mean	% + take	% No take
2 (99)*	4·18	2·35	0·42 / 0·06	..	..
3 (99)	6·75	2·65	1·13 / 0·01	24	76
4 (96)	8·1	3·35	1·8 / 0·02	82·8	17·2
5 (76)	10·3	4·15	2·3 / 0·28	91·9	8·1
6 (49)	11·2	4·65	1·3 / 0·2	91·9	8·1
7 (34)	10·55	4·67	0·83 / 0·06	91·9	8·1

*Number within parentheses indicate total number of babies available on the day

†Calculations based on figures at column 2 (Eryth)

The vaccinations were made on the lateral aspect of the left thigh at one point. After proper preparation of the skin the vaccine was introduced intradermally by a tuberculin syringe. The volume of the inoculum was 0·1 ml containing $1·5 \times 10^6$ virus particles.

It was difficult for reasons already stated, to follow up all vaccinated babies to a period of one week to categorise results of vaccination as 'Major' or 'Equivocal' as has been advocated (WHO 1964). However since vesiculation surrounded a zone of erythema appeared fairly early, there was no difficulty in recognizing cases where the vaccination was successful or unsuccessful. The successful cases have been described as 'Positive take' and unsuccessful cases as 'No take' in this communication.

Follow up : Following vaccination observations were made daily till the day of discharge, with particular emphasis on (*a*) extent of the vaccinial lesion, (*b*) day of transition from one stage to another, (*c*) rise in temperature, (*d*) regional lymphadenitis and any other complications. The room temperature of the nursery varied between 29·8°C and 31·5°C. Vesicular fluid was collected at random from a few subjects to confirm viral multiplication at the site. To minimise technical and observational errors all vaccinations and subsequent follow up were done by one of the authors (S.R.).

Results

Evolution of the vaccinial lesion : Erythema around the vaccination site was a noticeable feature in all cases where the vaccination ultimately was recorded as 'Positive take' and was conspicuously absent in the rest. In about 70% of the positive cases the zone of erythema was measurable and was associated with a centrally situated indurated area after a lapse of 48 h. The extent of erythema showed a gradual increase and attained the maximum diameter on the sixth day after vaccination. Specific vaccinial lesion subsequently replaced the indurated area as a papule or a vesicle. The vesiculation was early and could be seen in the majority on the 4th day (59·5%), a few on the 3rd day (7·6%) and on the 5th day (29·6%), of the total population. The transition from the induration to papular/vesicular stages, in many instances was rapid than would be anticipated normally, and the first noticeable vaccinial lesion seen was vesicular in many, the popular stage in these cases escaped notice altogether. The response pattern thus simulated 'Accelerated reaction' after revaccination. Among the vaccinated population who continued to stay in the hospital till the 7th day, the vesicular lesion progressed to pustular stage in only three. The statistical evaluation of the measurements is suggestive of an uniform pattern (Table I).

Effect of maternal vaccination status on the vaccination result : The data have been summarized in Table II. The number of babies born of mothers inlcuded in Groups A and E, were inadequate to merit any detail analysis. No significant difference in the 'take rate' among babies born of mothers of Groups B, C and D was evident. However, the general trend is suggestive of an association between successful take and maternal revaccination status. Higher percentage of 'Take' and earlier vesiculation was more often seen in the neonates born of mothers who were revaccinated in remote past. It may be noted the highest percentage of early vesiculation occurred in the same category.

Vesicular fluids collected at random from the lesions from individual cases were tested for the presence of virus and each yielded growth of vaccinia virus, on C.A.M.

Temperature recordings of the babies was normal in all cases (36°C to 36·8°C). Palpation of the regional lymph glands did not reveal any significant enlargement in any of the cases compared with the contralateral side. Admittedly, it appeared extremely difficult to differentiate minor enlargements. The neonates were singularly free from any complications beside allergic rash in two which disappeared without any medication with in 72 h and jaundice in one case. This was detected on the 3rd day and was considered physiological by the clinician. Special mention may be made with regard to one case, where exchange transfusion was resorted due to Rh-incompatibility. This baby also had a positive take, although the vesiculation was delayed till the 6th day. The donor's vaccination status was not known.

Table II. Influence of mother's vaccination status on the character of the vaccinial lesion

Mother's last revaccination	Number of babies vaccinated	Average date of apperance of vesicle	Number showing vesiculation on day			Average diameter of the lesion at its maximum in mm	'take' positive
			3	4	5		
(A) *During pregnancy	3	4·5	..	1	1	10·00	66·6
(B) Between 1 y—2 y	53	3·8	2	29	17	11·25	88·6
(C) Between 2 y—3 y	23	3·5	1	17	4	11·35	95·6
(D) Between 3 y—6 y	17	3·1	3	10	3	11·30	94·1
(E) 6 y or	3	3·0	1	2	—	11·50	100·0
Pooled	99	3·6	7	59	25	11·10	91·9

*Mother's groupings according to their revaccination status.

The total percentage of 'positive take' was 91·9. Amongst the 'no take' cases, mother of one baby was successfully revaccinated either at the commencement or just prior to the conception. Five were born of mothers included in Group B, two were born of mothers in Groups C and D, one each. The result from revaccination as could be gathered from the history were unsuccessful in all cases. The techniques seemed to be faulty in two, one in Groups B and D, as the virus was found deposited in the subcutaneous tissue instead of being intradermal. Incidentally, the study population included a twin. In conformity with the general acceptance, twins having identical consititutional make up, the evoluation of the vaccinial lesion was also indentical.

Discussion

Immunization programme include a long list of prophylactic measures shortly after birth. Attempts are being made to integrate the schedule in a manner which would cover all in least time and avoid too frequent parenteral administration (Hillary **et al** 1962, WHO 1968). Prophylactic vaccination against smallpox is in vogue for long. A reliable index to the success of any vaccination programme is the proportion of the preschool children who have been successfully vaccinated. Social customs

forbid such measures at many places, in addition, such population quite often is the hardest group to reach. They, therefore, constitute the bulk of the susceptibles and man also plays a major role as disseminator. Primary vaccination immediately after birth in an institute will minimise frequent home visits considered indispensable to assess the result.

The percentage of 'no take' results in this series is small and compares well with the experiences of the previous workers (Lin and Hyg 1965, Sil and Roy 1968). Lin and Hyg reported 21·5% failure in a series of new borns who received simultaneous B.C.G and smallpox vaccination ; and in the Hong Kong study as reported by them the failure rate was only 6·4%. Sil and Roy (1968) reported 17·6% failure. The method of vaccination in these studies was by scarification. It is interesting to note that in the 'no take' population erythema was notably absent. The absence of erythema in this population and its consistent presence and progressive increase in the extent in the successful cases, point towards a possible relationship of erythema with local replication of virus.

The general reluctance to immunize infants shortly after birth is due to an impression of adequate protection acquired from the mother (Espmark and Rabo 1965) and unknown hazards which may eventually occur. That such transfer of maternal antibody occurs across the placenta is well documented (Hale and Lee 1954, Kempe and Benenson 1953, Perkins **et al** 1958, Gelfand **et al** 1960). However, instance of viral infection in utero or shortly after birth (Narayan Rao **et al** 1954, Schaffer **et al** 1954) question the efficiency of such transfer in terms of protectivity. The best index of protection is freedom from the disease in the midst of an epidemic. In smallpox a challenge with a potent vaccine resulting in unsuccessful take, is also considered a sure evidence of protection (WHO 1968). Therefore, the results obtained in this study and other studies mentioned before (Lin and Hyg 1965, Sil and Roy 1968) would suggest that the level of passively acquired antibody may be inadequate quantitatively or qualitatively or both, for such generalization and that its presence do not antagonize successful evolution of dermal vaccinial lesion following primary vaccination. The efficiency of vaccination at this period of life in terms of its immunizing effect may rightly be questioned. Previous workers (Lin and Hyg 1965) revaccinated the infants in their series, as a challenge and noted that the majority of the babies who responded successfully on primary vaccination were refractory to revaccination. Immunizing effect is dependent on the extent to which virus multiplies at the site and that such multiplication do occur has been confirmed in this series.

Success after primary vaccination, apart from the passively acquired antibody, would depend on (a) potency and stability of the vaccine and (*b*) proper implantation of the vaccine virus and its replication in the host. In vaccinating newborns, it has been recommended to use vaccine 5 to 10 times more potent than standard vaccine to achieve success (Espmark 1965). Millar and Roberto (1964), in a study noted high 'take rate' in spite of using vaccine of lower potency, by implanting the vaccine by jet puncture a method closely similar to the intradermal route employed in this study. The significant difference between the classical methods of vaccination, such as

scarification, multiple pressure etc. and intradermal deposition depend on (*a*) volume of the vaccine actually used and consequently the extact number of viral particles and (*b*) easy recognition of efficient implantation. In the former methods the volume used is arbitrary and likely to differ from case to case. They also suffer from other defects, e.g. autoinoculation, wiping and washing out of the vaccine lymph and even to an expert vaccinator implantation remain principally a guess and supreme confidence on experience. In addition intradermal method may channelize effective utilization of vaccine hitherto considered as of low potency in a restricted manner.

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