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IMPACT OF VITAMIN A SUPPLEMENTATION ON CHILDHOOD MORTALITY
A Randomised Controlled Community Trial

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Summary 450 villages in northern Sumatra were randomly assigned to either participate in a vitamin A supplementation scheme (n=229) or serve for 1 year as a control (n=221). 25 939 preschool children were examined at baseline and again 11 to 13 months later. Capsules containing 200 000 IU vitamin A were distributed to preschool children aged over 1 year by local volunteers 1 to 3 months after baseline enumeration and again 6 months later. Among children aged 12–71 months at baseline, mortality in control villages (75/10 231, 7·3 per 1000) was 49% greater than in those where supplements were given (53/10 919, 4·9 per 1000) ($p<0·05$). The impact of vitamin A supplementation seemed to be greater in boys than in girls. These results support earlier observations linking mild vitamin A deficiency to increased mortality and suggest that supplements given to vitamin A deficient populations may decrease mortality by as much as 34%.

Introduction

A LONGITUDINAL observational study in rural central Java indicated that children with ocular signs of mild vitamin A deficiency were more likely than neighbourhood controls to die, that mortality was directly related to severity of vitamin A deficiency, and that poor survival was probably attributable, at least partly, to high rates of respiratory disease and diarrhoea.[1-3] We report here the results of a randomised, controlled, community trial of vitamin A prophylaxis in northern Sumatra.

Subjects and Methods

The study was carried out in Aceh Province, which is at the northern tip of Sumatra and where xerophthalmia is prevalent.[4,5] The population is ethnically distinct from that of Java, where the earlier observational study had been conducted.[1-3]

For political and administrative reasons a cluster sampling scheme was employed. The sampling frame consisted of 2048 villages in Aceh Utara and Pidie, two contiguous rural kabupatens (districts) chosen because they had no current or planned development projects or vitamin A supplementation schemes. From a random start, 450 villages were systematically selected for the study; these were then randomised for capsule distribution after the baseline examination (programme villages, n=229) or after the follow-up examination (control villages, n=221). 18 villages from among those still in the sampling frame were substituted for adjacent villages found to have started vitamin A supplementation before the baseline survey.

All members of the two study teams, each consisting of an ophthalmologist (team leader), a nurse, an anthropometrist, a dietary interviewer, five enumerators, and a driver, all fluent in the local dialect received a month's classroom, hospital, and field training. The enumerators, responsible for collecting demographic data, were unaware that mortality was a research question. Standardisation exercises were done before and regularly throughout the study. First, each village was visited to identify households containing children aged 0–5 years and to mark their dwellings. Within 2 days the village was visited by the full team. Enumerators visited every house containing preschool children, collected socioeconomic, demographic, and medical data, and rounded up children at a central point for their clinical examination. Dates of birth were ascertained by reference to local events charted on the Muslim calendar and then translated to their roman equivalent by the use of a specially prepared conversion table. Eyes were examined with a focused light and 2X loupes and diagnoses were made according to standard diagnostic criteria.[5,6] Parents were carefully questioned about the presence of nightblindness.[5,7] They were also asked about a history of diarrhoea (4 or more loose, watery stools per day), of fever or cough lasting at least 24 h in the previous 7 days, and of "ever having" measles.

Recumbent length (if less than 24 months old) or standing height (if 24 months or older) to the nearest 0·1 cm, and weight (using a calibrated Salter scale) to the nearest 0·1 kg, were measured on a 10% subsample of all study children.

All children with active xerophthalmia at baseline examination received at least one large dose of vitamin A and were referred to the local health unit. They were excluded from the analyses of subsequent morbidity and mortality. All children received vitamin A at the follow-up examination 9–13 months later.

Teams first visited villages between September, 1982, and August, 1983, and follow-up visits were made by the same team in the same sequence 9–13 months later. The variation in follow-up time resulted from attempts to minimise the potential confounding influence of the Muslim fasting month and post-fasting holidays.

Standard capsules (supplied by UNICEF) were given to every child aged 1–5 years in programme villages, by a local volunteer trained to do so. The capsule nipple was snipped off and the contents (200 000 IU vitamin A and 40 IU vitamin E) were expressed into the child's mouth. This volunteer kept a list of children treated and issued the household with a distribution card. The first dose was given 1–3 months after the baseline examination and the second 6–8 months later. A distribution monitor visited each village 2–4 weeks after the scheduled distribution and interviewed 10% of eligible households. If coverage was less than 80% the local distributor was encouraged to reach children previously missed.

All data were collected on precoded forms, entered onto diskettes, and shipped to the data management facility at the International Center for Epidemiologic and Preventive Ophthalmology, Johns Hopkins University, where the information was processed with the SIR data management package run on an IBM 4341 computer. Statistical analyses were made with SIR, SAS, and GLIM software. Statistical tests for significance and development of confidence intervals were adjusted for clustering associated with randomisation by village rather than by individual, and for the small number of events expected and observed in any one village by applying poisson regression with extra-poisson variation to account for natural variability in mortality among villages.[8,9] Two-tailed tests were used.

The study was designed to examine overall differences between non-infant preschool-age children in programme versus control villages, on the assumption that mortality would be reduced by at least 20% and allowing for an alpha error of 0·05 and a beta error of

0·2 (1-tailed). Stratified subgroup analyses are, strictly speaking, inappropriate, and, because of the small numbers, not very reliable.

Although Indonesian government regulations proscribe administration of vitamin A prophylactically to infants, a considerable proportion of them received capsules nonetheless, so the impact on infant mortality was also examined.

All study procedures were approved by a steering committee consisting of representatives of the Indonesian Center for Nutrition Research, the Directorate of Community Health Services, the provincial health authorities, Johns Hopkins University, and Helen Keller International.

Results

29 236 preschool-aged children were enumerated at baseline. Follow-up information was available on 89·0% of the programme children and 88·4% of the controls. The age and sex distribution of children lacking follow-up was identical in the two groups.

Baseline Characteristics

Of the 25 939 children with baseline and follow-up information, details of the initial ocular examination are available for 91·9% of programme children and 90·5% of controls. Active xerophthalmia was more prevalent in controls than in the programme group (2·25 versus 1·88%), but the difference was not significant and was accounted for almost entirely by the males (table I). Xerophthalmia was more prevalent among males than females, especially among controls. Xerophthalmia prevalence was negligible during the first 2 years of life (less than 0·5%).

TABLE I—BASELINE PREVALENCE OF ACTIVE XEROPHTHALMIA

—	No of patients with: Night-blindness* (XN)	Bitot's spots* (X1B)	Active xerophthalmia* (XN, X1B, X3)
Total†			
Programme (n=12 281)	136 (*1·11%*)	143 (*1·16%*)	231 (*1·88%*)
Control (n=11 378)	150 (*1·32%*)	164 (*1·44%*)	256 (*2·25%*)
Males			
Programme (n=6043)	69 (*1·14%*)	72 (*1·19%*)	120 (*1·99%*)
Control (n=5583)	88 (*1·58%*)	102 (*1·83%*)	150 (*2·69%*)
Females			
Programme (n=5881)	66 (*1·12%*)	69 (*1·17%*)	108 (*1·84%*)
Control (n=5494)	61 (*1·11%*)	59 (*1·07%*)	103 (*1·87%*)

*Prevalence rates for XN and X1B are not mutually exclusive. For "active xerophthalmia" an individual was counted only once. There were only 6 patients with corneal ulceration (X3), 3 in each group. Conjunctival and corneal xerosis were excluded as being potentially less reliable.[9]
†Includes 357 programme and 301 control children whose sex was unknown.

TABLE II—AGE AND SEX DISTRIBUTION ON NON-XEROPHTHALMIC CHILDREN

—	Programme	Control
*Total**	12 991 (*100%*)	112 209 (*100%*)
Sex†		
Male	6365 (*50%*)	5975 (*50%*)
Female	6243 (*50%*)	5888 (*50%*)
Total	12 608 (*100%*)	11 863 (*100%*)
Baseline age (months)		
<12	2074 (*16·0%*)	1979 (*16·2%*)
12–23	1979 (*15·2%*)	1941 (*15·9%*)
24–35	2086 (*16·1%*)	2072 (*17·0%*)
36–47	2274 (*17·5%*)	2016 (*16·5%*)
48–59	1887 (*14·5%*)	1724 (*14·2%*)
60–71	2686 (*20·7%*)	2465 (*20·2%*)
Total	12 986 (*100·0%*)	12 197 (*100·0%*)

*Includes infants, as well as children on whom age and/or sex are unavailable.
†Sex not known for some children.

The age and sex distributions of the non-xerophthalmic children in the two groups were similar (table II). The disproportionate number of children purported to be in the 6th year of life probably includes children really in their 5th and 7th years, as has been noted previously.[5] Programme and control children were also similar for most other baseline demographic and socioeconomic variables, including occupation of the head of the household, maternal education, source of drinking water, distance to the nearest elementary school, and distance to the nearest health centre.

The two groups were also similar in most health variables such as recent history of fever or cough or of ever having had measles; relative risks of these variables for the two groups differed by less than 5% (table III) except for diarrhoea, a recent history being 23% commoner among control than programme children (p=<0·05), with the greatest excess in girls. Recent diarrhoea was commonest during the 2nd year of life, when the frequency was 9·8% in programme villages and 10·7% in control villages. Thereafter it steadily declined. The most objective baseline health variable was nutritional status. Anthropometric indices were similar for the two groups, both total and sex-specific (table IV).[10]

In 99% of children in the two study groups, the interval between baseline and follow-up examination was at least 11 months, and for 59%, at least 12 months. This interval did not vary among age-sex-specific categories by more than ±2%.

Vitamin A Distribution Level

Of our three methods of monitoring for capsule administration only interrogation of the child's guardian(s) proved feasible. Report forms provided by the local distributors were largely illegible, and most cards issued to households were faded, torn, or lost.

Over 93% of preschool children (12–71 months at baseline) living in programme villages received at least one large dose of vitamin A between baseline and follow-up examinations;

TABLE III—BASELINE MORBIDITY VARIABLES

—	Programme Total no	Programme % positive	Control Total no	Control % positive	Relative risk compared with that for control
Cough*	12 781	31·2	11 555	32·7	1·05
Fever*	12 781	45·7	11 555	46·7	1·02
Measles†	11 753	22·3	10 059	21·7	0·97
Diarrhoea*	12 781	7·1	11 555	8·7	1·23

*Present in past seven days. Data missing on 210 programme children and 654 controls.
†Any time in past. Smaller denominator because of change in question shortly after survey began.

TABLE IV—BASELINE ANTHROPOMETRY

—	Programme (n=1382)	Control (n=1271)
*Height for age (% of median)**		
<85†	8·2%	8·9%
85–89	23·9%	27·6%
90–94	43·0%	37·8%
⩾95	24·9%	25·7%
*Weight for height (% of median)**		
<80	3·0%	3·7%
80–89	38·3%	35·6%
⩾90	58·6%	60·7%

*Median NCHS standards.[11] Represents 10% subsample of children.
†Less than 1·5% of children in either group were below 80% of median.

TABLE V—NUMBER* REPORTED TO HAVE RECEIVED VITAMIN A CAPSULES DURING FOLLOW-UP

Age (months) at baseline	Programme villages		Control villages	
	At least 1 capsule	2 capsules	At least 1 capsule	2 capsules
2–23	1899 (*93·1*)	1854 (*77·7*)	1707 (*0·7*)	1895 (*0·2*)
4–35	2007 (*93·3*)	1946 (*78·1*)	1792 (*1·2*)	2010 (*0·1*)
6–47	2192 (*94·0*)	2130 (*78·7*)	1771 (*1·3*)	1956 (*0·2*)
8–59	1806 (*93·5*)	1765 (*78·4*)	1509 (*0·7*)	1683 (*0·1*)
0–71	2593 (*92·4*)	2528 (*77·5*)	2121 (*1·2*)	2400 (*0·2*)
Total	10 497 (*93·2*)	10 223 (*78·1*)	8900 (*1·1*)	9944 (*0·2*)
<12	1968 (*82·4*)	1879 (*61·8*)	1728 (*1·1*)	1914 (*0·1*)
Respondent uncertain about capsules	259	259	130	130
Information unavailable	260	623	1438	208

*Number of those for whom information was complete (age not known for 7 other programme children and 13 other controls).
Numbers in parentheses are percentages.

78% received two doses (table V). In every age-group coverage of boys and girls differed by less than 1%.

In theory, only two-thirds of the infants were eligible for one capsule and less than one-quarter for two. Surprisingly, 82% received at least one capsule and almost 62% both. This discrepancy may reflect disregard of normal government guidelines or of small differences in age.

Only 1% of control subjects received any capsule, presumably obtained at the health centres by children presenting with xerophthalmia.

Impact on Xerophthalmia and Mortality

The prevalence of active xerophthalmia in programme villages declined from 1·9% at baseline to 0·3% at follow-up and that in the control villages declined from 2·3% to 1·2%. These changes meant that the risk of xerophthalmia in control villages relative to that in programme villages rose from 1·2 at baseline to 4·0 at follow-up ($p<0·05$). Sex-specific prevalence rates followed a similar pattern.

During the follow-up period 75 preschool study children from control villages and 53 from programme villages died, giving mortality rates of 7·4 and 4·9 per 1000, respectively ($p<0·05$, two-tailed) (table VI). The relative risk of dying in control versus programme villages was therefore 1·51 (95% confidence limits 1·03, 2·28), equivalent to a reduction in mortality in programme villages of 34%. Infants in control villages had a mortality rate 21% greater than those in programme villages.

To compare age/sex/study group-specific mortality, children were classed as preschool children and infants (table VI). Both infant and preschool control boys died 70% more frequently than did those in the programme villages. The relative risk of death for boys in control versus programme villages was 1·69 (95% confidence limits 1·14, 2·51). Excess mortality was less pronounced among control girls, in whom it was limited to preschool children.

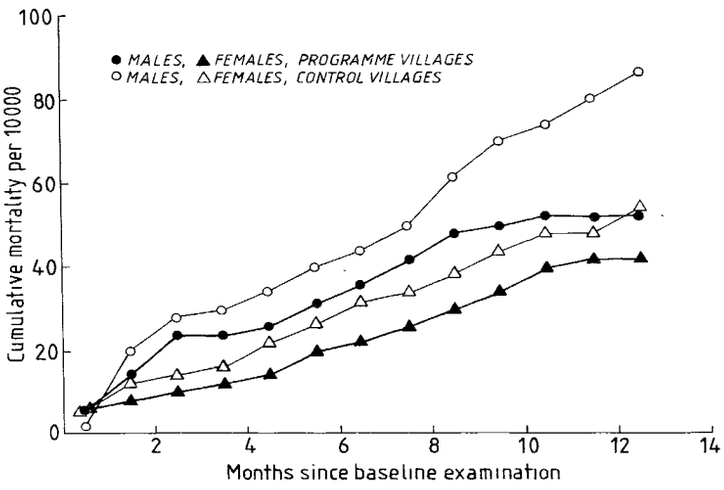
To examine further the effect of large doses of vitamin A on mortality, cumulative sex-specific mortality rates for pre-school children were calculated every month after baseline examination (see accompanying figure). Boys and girls show similar patterns: mortality in control villages was initially the same as (females) or lower (males) than that in programme villages; with time, mortality in control villages gradually

TABLE VI—AGE AND SEX-SPECIFIC MORTALITY DURING FOLLOW-UP

Baseline age (months)	Programme villages		Control villages		
	Proportion dying	Rate per 1000	Proportion dying	Rate per 1000	RR
Both sexes					
12–23	19/1979	9·6	22/1941	11·3	1·17
24–35	14/2086	6·7	25/2072	12·1	1·81
36–47	11/2274	4·8	8/2016	4·0	0·83
48–59	5/1887	2·6	7/1724	4·1	1·58
60–71	4/2686	1·5	13/2465	5·3	3·53
Total preschool*	53/10 917	4·9	75/10 230	7·4	1·51 (1·03, 2·28)‡
Infants (<12)	48/2074	23·1	55/1979	27·8	1·21 (0·73, 1·97)‡
Total* (0–71)	101/12 991	7·8	130/12 209	10·6	1·36 (1·01, 1·85)‡
Males†					
0–11	18/1014	17·8	29/970	29·9	1·68
12–71	28/5348	5·2	44/4998	8·8	1·69
Total (0–71)	46/6362	7·2	73/5968	12·2	1·69 (1·14, 2·51)‡
Females†					
0–11	28/994	28·2	25/942	26·5	0·94
12–71	23/5245	4·4	27/4933	5·5	1·25
Total (0–71)	51/6239	8·2	52/5875	8·9	1·09 (0·71, 1·71)‡

*Includes children with age unknown
†Excludes children for whom age and/or sex are unknown.
‡95% confidence limits.

exceeded mortality in programme villages, a trend which was more pronounced in boys; by the end of the follow-up period, 2–4 months after the second dose of vitamin A, cumulative mortality had reached a plateau in programme villages, but it continued to climb in control villages. The pattern among infant boys mimicked that of preschool boys. Cumulative mortality among infant girls in control villages was virtually indistinguishable from that in programme villages.



Cumulative sex-specific mortality at monthly intervals after baseline examination for preschool children (aged 12–71 months at baseline examination).

First dose given during months 1–3; second a mean of 6 months later.
Males—denominator for first 12 months in programme villages, 5351 (no further deaths); in control villages, 5005 initially, 3046 during the last month.
Females—denominator for first 12 months in programme villages, 5249 (no further deaths); in control villages, 4946 initially and 2978 during the last month.

Discussion

Mortality rates have been reported to be higher in malnourished children in hospital with xerophthalmia than in those with normal eyes.[11,12] However, another study has shown that in children admitted to hospital for xerophthalmia, severe malnutrition was the most important factor associated with mortality.[5] Interpretation of these studies is hindered by the biases inherent in family motivation and hospital admission criteria, and the impact intensive therapy has on mortality.

In a longitudinal study of 4000 preschool-aged Javanese children we found that children with mild xerophthalmia (night blindness, Bitot's spots, or the two conditions together—a ranking shown to be closely correlated with serum vitamin A levels[5,7]) died at four times the rate for their non-xerophthalmic peers; the excess mortality was related to the severity of the xerophthalmia; and this "dose-related" risk was independent of the child's general nutritional status.[1,2] The shape of the dose-response curve suggested that subclinical vitamin A deficiency (ie, in the absence of detectable xerophthalmia) was also associated with increased mortality. Follow-up of surviving children revealed that respiratory and diarrhoeal diseases were 2–4 times more likely to have developed in those who had been xerophthalmic than in their non-xerophthalmic peers.[3] Again, vitamin A status seemed to be more important than anthropometric status in predicting morbidity.

The present study was thus undertaken, partly to determine whether supplements of vitamin A given to preschool children (12–71 months of age) would reduce their mortality by at least 15%. Ideally all "treatment" children would have received at least the recommended daily allowance. But this would have required a special, impracticable delivery system. Instead we opted for the regular Indonesian government scheme of twice-a-year administration of UNICEF-supplied capsules by trained local volunteers, although we realised that it did not cover infants. The Government of Indonesia would not condone the use of placebos but field-workers collecting demographic data were unaware that mortality was a research issue.

Strict randomisation of the 450 study villages seemed to have worked reasonably well. The populations were similar in most baseline characteristics investigated except for xerophthalmia and history of recent diarrhoea, which were slightly more prevalent among the controls. The differences between programme and control populations in mortality were out of proportion to their baseline differences; the baseline difference in diarrhoeal history was greatest for females, whereas excess mortality was greatest for males; and the most objective, quantifiable baseline indices of health status, weight-for-height and height-for-age, were virtually identical in the two groups on both an age and sex specific basis.

There was no evidence during the course of the study of differences in economic or medical initiatives in the study area, though clearly the vitamin A status throughout the province was improving as shown by a substantial reduction in prevalence of xerophthalmia between the 1978 nationwide survey and the baseline examination in the present study. The reduction in prevalence of xerophthalmia in control villages during our study may have been part of the general spontaneous improvement, which is the reason for having controls.[5,6] The mortality rates in this study were also lower than previously recorded for Java,[13] where rates seem to be falling, and more closely resemble those of neighbouring "medium" infant mortality rate countries (eg, Philippines, Malaysia, Thailand), where the median mortality in preschool-aged children is 3 per 1000.[14]

Results were strongly positive, even in this "intent-to-treat" analysis. Xerophthalmia prevalence among preschool children living in programme villages declined by 85%, a result similar to those obtained in other carefully conducted pilot trials,[5,15-17] and it confirms the high distribution rate of capsules reported. Preschool control children died 1·5 times more frequently than did programme children (95% confidence limits 1·03, 2·28), equivalent to a 34% reduction in non-infant mortality among residents of programme villages. To control for baseline differences in prevalence of xerophthalmia and history of recent diarrhoea between programme and control villages, the proportion of children with xerophthalmia or recent history of diarrhoea at baseline was included as a covariate (predictor variable) in the analysis. Mortality results (relative risks and their confidence limits) were nearly identical when either xerophthalmia alone or when both xerophthalmia and diarrhoea were included in the analysis.

Although the study was not designed to investigate subgroups, and the numbers concerned preclude definite conclusions, they provide additional evidence consistent with the beneficial impact of vitamin A supplementation: mortality among controls was greater at almost every age, including the first year of life; the difference in cumulative mortality increased with time, even though male and female controls had initial mortality rates that were the same as or lower than those in programme villages; the impact was greatest among boys, in whom vitamin A deficiency is generally far more prevalent;[5,17-20] and among boys, the time-related mortality pattern corresponded with the expected temporal impact of capsule distribution. This internal consistency and agreement with previous studies is more important than the size of the p value or width of the confidence limits, which are direct consequences of the enormous sample size required.

These results are especially encouraging for the following reasons: capsule distribution was less than universal and probably missed those who needed it most;[21] single large-dose supplementation maintains raised serum vitamin A levels for only 1–3 months;[22] distribution did not start until 1–3 months after enumeration; xerophthalmic controls took vitamin A at health centres; and those in whom the greatest impact might have been expected (children xerophthalmic at baseline) were treated and dropped from the analysis.

How vitamin A reduces mortality remains uncertain. Vitamin A deficiency is associated with changes in surface epithelium and these may disrupt normal barrier function, support bacterial growth (as seen on the conjunctiva[23] and presumably the bladder[24]), and obstruct smaller branches of the tracheobronchial tree. Abnormalities in systemic immune competence associated with vitamin A deficiency may also be as important in contributing to mortality; in animals at least, vitamin A deficiency interferes with humoral and especially cell-mediated immunity.[25-27] Limited data suggest similar effects in man.[28] High doses of vitamin A given to otherwise normal animals have been reported to produce a non-specific, adjuvant-like increase in resistance to infection.[29] The response to the high doses given in our study was unlikely to be due to non-specific changes. The children came from a vitamin A deficient population[5,7] and the impact was

sustained. The rise in blood retinyl ester levels after one large dose of vitamin A given to deficient patients do not last for more than 8–12 weeks;[22,30] and holo-retinol-binding-protein levels rise, but not above normal levels.[30,31]

The presence of the study teams was unlikely to have influenced the results of our study because the only difference between programme and control villages in their interaction with study personnel consisted of at most two contacts in 12 months with the local vitamin A distributor in treatment areas. This distributor was neither trained nor instructed to undertake any other intervention.

Vitamin A status probably modulates the incidence and severity of disease caused by a variety of pathogenic organisms. The impact that vitamin A supplementation will have on mortality will therefore depend upon a constellation of factors, including the prevalence and severity of vitamin A deficiency; the frequency of exposure to pathogenic organisms, size of the inoculum, and their virulence; and the presence and degree of other adverse influences with which the young child must contend (eg, malnutrition, parasitic load). The results of the study reported here and those done in Java[1-3] confirm the importance that vitamin A deficiency in childhood has on mortality in Indonesia and show the impact that supplementation can have on child survival.

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The Aceh Study Group includes the following professional staff, apart from those listed as authors: Dr Akbar Pandji, Dr Koesdiono, Dr Daniel Kraushar, and Dr Hugh R. Taylor, Barbara Hawkins, Imam Satibi, and William Flumenbaum. Dr Scott Zeger developed the statistical methodology.

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PRE-OPERATIVE IDENTIFICATION OF PATIENTS AT HIGH RISK OF DEEP VENOUS THROMBOSIS AFTER ELECTIVE MAJOR ABDOMINAL SURGERY

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Summary Eighteen items of clinical and laboratory information were measured on the day before operation in 85 patients who underwent elective major abdominal surgery. Postoperatively, deep venous thrombosis (DVT) was detected by ^{125}I-fibrinogen scan in 23 patients. Stepwise logistic discriminant analysis was used to identify factors which predicted DVT. Seven such factors were identified, which were then used to construct a predictive index. In descending order of predictive power, they were: age, euglobulin lysis time (ELT), previous abdominal surgery, varicose veins, antithrombin III concentration, cigarette smoking, and platelet count. Pre-operatively, the predictive index correctly identified 91% of the patients in whom DVT developed, and wrongly allocated to the high-risk group 19% of those in whom it did not. A shortened version of the predictive index based only on age and ELT ($I = -11{\cdot}5 + 0{\cdot}133$ age $+ 0{\cdot}006$ ELT) was 91% sensitive and 63% specific in the prediction of DVT. In a prospective study of 43 patients, this shortened predictive index correctly identified pre-operatively 93% of patients in whom DVT developed, and wrongly allocated to the high-risk group only 17% of those in whom it did not.

Introduction

DEEP venous thrombosis (DVT) develops in approximately 30% of general surgical patients after elective major abdominal surgery.[1,2] Prophylactic measures, such as the administration of low-dose heparin or dextran, significantly reduce the frequency of postoperative deep venous thrombosis and pulmonary embolism.[3-5] However,

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