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EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI NELL'INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction ($p=0·0002$, relative risk 0·81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

Introduction

THE trial of the Italian Group for the Study of Streptokinase in Myocardial Infarction (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico, GISSI) was planned in autumn, 1983. At that time there was a growing consensus on the effectiveness of intracoronary streptokinase (SK) in reopening occluded coronary vessels in around 50–60% of treated patients;[1] and analysis of pooled data suggested that intravenous SK, given in various schedules, could reduce overall mortality in patients treated within 24 h from onset of pain.[2] The clinically relevant challenge was therefore to test in a formal prospective trial whether effective and safe thrombolysis could be achieved with intravenous SK under routine conditions in the majority of patients—in contrast to intracoronary thrombolysis which is practicable only in small numbers of cases.[3]

The participation of the majority of the coronary care units (CCUs) grouped in the National Society of Hospital Cardiologists (Associazione Nazionale Medici Cardiologi Ospedalieri, ANMCO) was sought, to ensure recruitment over an acceptable length of time of the large sample needed to test reliably three key issues: Does intravenous SK infusion produce a clinically relevant benefit in terms of reduction of in-hospital and one-year mortality? Is the effect, if any, dependent on the interval from onset of pain to SK treatment? Are the risks associated with the treatment acceptable?

Patients and Methods

The study was planned as a controlled multicentre unblinded trial with central randomisation. Fig 1 summarises the major steps. The only variable distinguishing the treatment group (SK) from the

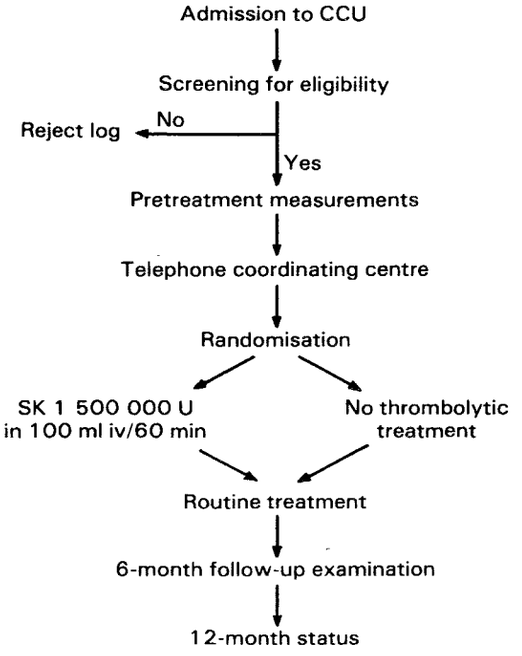

Fig 1—GISSI protocol.

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control group (C) was intravenous infusion of 1·5 million units of SK in 100 ml physiological saline in 1 h. The protocol did not require modification of the diagnostic and therapeutic practice of the participating CCUs. Specifically, since it was not universally practised, anticoagulant treatment was not considered as part of the protocol and was left to the choice of each CCU: the recommendation was that, when the policy of the CCU included anticoagulation, the same regimen should be given to SK and C patients. Patients were judged eligible (*a*) if they had chest pain accompanied by ST segment elevation or depression of 1 mm or more in any limb lead of the electrocardiogram (ECG) and/or of 2 mm or more in any precordial lead; and (*b*) if they were admitted to the CCU within 12 h from the onset of symptoms. Absolute contraindications to treatment with SK were recent or current bleeding; cerebrovascular accident within the previous 2 months; a surgical procedure or trauma within the previous 10 days; invasive procedures (eg, percutaneous biopsy, subclavian puncture) within the previous 10 days;[4] uncontrolled hypertension (systolic ⩾200 mm Hg, diastolic ⩾110 mm Hg); previous treatment with SK; any other life-threatening condition concomitant with myocardial infarction (MI). Relative contraindications were very recent external cardiac massage; suspected presence of thrombi in the left side of the heart (eg, mitral valve disease with atrial fibrillation known haemostatic disorders, including those associated wit severe renal or hepatic failure; bacterial endocarditis; pregnanc and haemorrhagic diabetic retinopathy.

Eligible patients were randomised by telephone call to th coordinating centre, which operated 24 h a day. Treatment wa assigned from a computer-generated list that allowed blocking an stratification by hospital. At randomisation the following data c the patient were collected: name, date of birth, sex, time from ons of symptoms, blood pressure, previous MI. At discharge from th CCU, information on the main prognostic factors, clinic evolution, and therapy were collected on a single form. Aft discharge from hospital a second form summarising in-hospit major clinical events and discharge therapy was filled out. All th material, together with the prerandomisation ECG, was sent to th coordinating centre. The complete clinical record was mad available for those patients who died in hospital. A log was kep containing essential information on patients admitted to th participating CCUs but not randomised in the trial.

The sample size of about 12 000 patients to be randomised wa estimated according to the following criteria: initial estimate c baseline MI mortality 12%; expected reduction in overall mortalit as a consequence of SK treatment 20%; significance level 1% an power 95%. The protocol specified three interim analyses, at 300(6000, and 9000 recruited patients. Results from these wer presented to the ethics committee only; a difference in mortalit exceeding three standard deviations or an unacceptably hig incidence of adverse reactions to SK would have led the committe to call an early halt to the trial.

The research protocol, approved by the ethics committee of th regional health authority, did not require informed consent- mainly because the patients' predicament was judged too acute fo acceptable application of the procedure. Medical staff were ready t provide explanations to the patients upon request.

The results presented in this report refer to the in-hospital perio only (which was 14–21 days in over 90% of patients and the same i the two groups) and are analysed on the principle of "intention t treat". At this stage it is not necessary to use survival analys techniques. Where appropriate, the statistical significance c observed differences has been assessed with χ^2 and t tests. Result are also illustrated by means of relative risk (RR) estimates. Th only subgroup analysis explicitly planned by the protocol was th stratification of the population according to the time elapsed fro the onset of symptoms to randomisation (0–3, >3–6, >6–9 >9–12 h).

TABLE I—BASELINE CHARACTERISTICS OF PATIENTS ON ADMISSION AND PROGNOSTIC FACTORS

	SK No=5860	C No=5852
Females (%)	19·7	19·7
Age in yr (%)		
⩽65	65·2	64·6
>65–75	24·6	24·6
>75	10·1	10·6
Not reported	0·1	0·2
Time (h) from onset of symptoms to randomisation (%)		
⩽3	51·5	52·6
<3–6	31·5	30·7
>6–9	11·8	11·3
>9–12	5·0	5·2
Uncertain	0·2	0·2
Systolic blood pressure (mm Hg) at randomisation (%)		
⩽90	4·9	4·1
>90–150	71·3	73·0
>150	23·5	22·5
Not reported	0·3	0·4
Diastolic blood pressure (mm Hg) at randomisation (%)		
⩽90	72·2	73·6
>90–105	22·2	21·0
>105	4·2	3·9
Not reported	1·4	1·5
Site of infarct (%)		
Anterior	36·4	37·5
Inferior	34·2	34·2
Lateral	5·1	4·3
Multiple location	14·2	13·8
ST depression	3·8	3·9
Site undefined	5·5	5·7
Not reported	0·8	0·6
Previous infarct (%)		
No	83·7	84·1
Yes	15·8	15·2
Doubtful	0·3	0·5
Not reported	0·2	0·2
Killip scale (%)		
1	71·2	70·1
2	22·7	22·9
3	3·2	4·2
4	2·5	2·3
Not reported	0·4	0·5

TABLE II—CARDIOVASCULAR DRUGS ADMINISTERED IN HOSPITAL (%)

	SK No=5860	C No=5852
Heparin iv and oral anticoagulants	21·5	20·8
Heparin, low-dose sc	40·8	41·7
Nitrates		
Iv	35·8	38·4
Oral	32·3	33·5
Calcium antagonists	47·2	49·5
Antiplatelets	13·0	14·7
Antiarrhythmics	35·9	34·0
Beta-blockers	8·3	8·3

TABLE III—BASELINE CHARACTERISTICS OF PATIENTS ON ADMISSION TO CCUs DURING STUDY PERIOD BUT NOT RANDOMISED (20 020)

—	Proportion
Female/male	5552/14 468
Deaths (female/male)	1024/1483
Age in yr (%)	
⩽65	48·5
>65–75	28·4
>75	20·9
Not reported	2·2

ECG tracings were analysed blindly by an independent committee to assign infarct sites according to the following criteria:

Anterior MI.—Q wave and/or ST elevation ⩾2 mm in V_1 through V_6.

Inferior and/or posterior MI.—Pathological Q wave duration ⩾0·03 s; voltage ⩾¼ of R in aVF) and/or 1 mm ST elevation in II, III, and aVF; rS in III with absence of R in II and/or aVF; R ⩾S in V_1 or V_2 with respect to a previous ECG, or with a lower voltage R in the following precordial leads.

Lateral MI.—Pathological Q wave (duration ⩾0·04 s and voltage ⩾¼ of R) in I and aVL or in V_5 and V_6.

Site undefined.—Bundle branch block with secondary alterations of the repolarisation masking pathological Q waves and ST alteration.

Multiple sites.—Concomitant signs of anterior or lateral and inferior MI without a history of previous infarct.

MI with ST depression.—ST depression ⩾1 mm in one or more peripheral leads or ⩾2 mm in one or more precordial leads.

Medical records of dead patients were analysed by an ad-hoc committee of two cardiologists blind with respect to treatment assignment, to assess and classify the cause of deaths. A similar procedure was applied to the analysis of cerebrovascular accidents. Details on the findings of these analyses with respect to the timing of the fatal and non-fatal events and to their relation with concomitant treatments will be reported elsewhere. Results obtained on end-points other than the ones specified by the protocol have to be regarded as hypothesis-generating rather than definitive.

Results

A total of 11 806 patients were randomised in one hundred and seventy-six participating CCUs (from a national total of about two hundred) homogeneously distributed over Italian territory and over a period of 17 months (February, 1984, to June, 1985). Recruitment was constant, at a rate of about 700 patients per month; 47% of the CCUs randomised fewer than 50 patients, 33% between 50 and 100, and 20% more than 100. 5905 patients were allocated to the SK group and 5901 to the control group.

The data sheets of 94 randomised patients (45 SK and 49 C) could not be traced. The baseline characteristics, collected at randomisation, of these "missing" patients (who constituted only 0·9% of the total) closely correspond to those of the sample analysed. Small discrepancies in the totals of the tables are explained by lack of some information on a few patients.

Table I shows that, in terms of baseline characteristics and prognostic factors, the two arms were adequately balanced. The size of the sample should guarantee homogeneity of the patients in the two groups even for characteristics that were not measured. There was very good balance in the use of concomitant treatments, as recommended by the protocol (table II).

Of all the patients admitted to the CCUs during the study

TABLE IV—OVERALL MORTALITY AND CAUSES OF DEATH

—	SK	C	p	RR (95% CI)	Total
% mortality	10·7	13·0	0·0002	0·81 (0·72–0·90)	11·8
Deaths/no of patients	628/5860	758/5852			1386/11 712
Causes of death					
CV	588	696			1284
Non-CV	32	45			77
Undefined	8	17			25

RR = relative risk; CI = confidence interval; CV = cardiovascular.

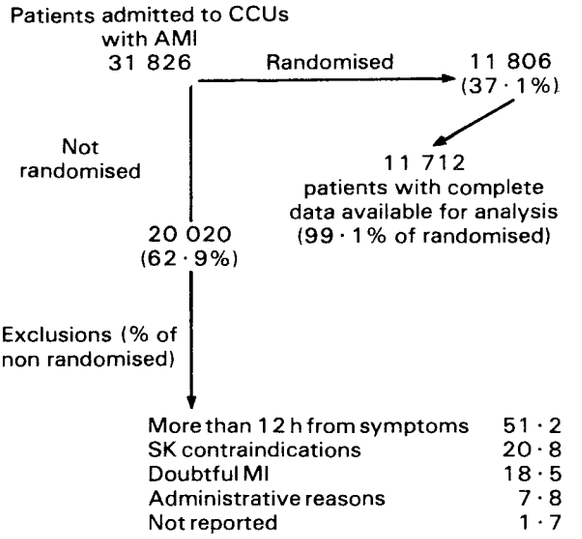

Fig 2—Registration of patients admitted to CCUs during study period.

period, 20 020 were not randomised and their characteristics are shown in table III. The reasons for exclusion as reported in the logs are summarised in fig 2. Absolute or relative contraindications to SK were judged present in 12·6% and 8·2%, respectively (for a cumulative 20·8%), of all patients admitted to the participating CCUs over the study period but not randomised.

At discharge, 94·2% of the 11 712 analysed patients had a confirmed diagnosis of acute MI and a further 2·8% of angina. The proportions with these diagnoses in the SK and C groups were the same.

Table IV summarises the main results of the study (with the principal causes of death); and table V gives results for the whole population stratified by hours elapsed before randomisation. SK treatment produced a statistically highly significant 18% decrease in the overall mortality of the whole population, and the beneficial effect was even more striking in the subpopulation treated soon after onset of pain; in those treated within 3 h overall mortality was reduced by 23%. Table VI shows the effects of SK on mortality according to sex and age.

The analysis of the subgroups obtained by stratifying the population according to infarct site and history of previous infarct (table VII) suggests beneficial effects from SK, reaching high statistical significance, in patients with anterior and multiple-site infarcts; SK patients with lateral infarcts or ST depression at entry did somewhat worse than controls, though the difference is not significant. The data also suggest

TABLE V—MORTALITY BY HOURS FROM ONSET OF SYMPTOMS

Hours	SK % (deaths/n)	C % (deaths/n)	p	RR (95% CI)	Total % (deaths/n)
⩽3*	9·2 (278/3016)	12·0 (369/3078)	0·0005	0·74 (0·63–0·87)	10·6 (647/6094)
>3–6	11·7 (217/1849)	14·1 (254/1800)	0·03	0·80 (0·66–0·98)	12·9 (471/3649)
>6–9	12·6 (87/693)	14·1 (93/659)	NS	0·87 (0·64–1·19)	13·3 (180/1352)
>9–12	15·8 (46/292)	13·6 (41/302)	NS	1·19 (0·75–1·87)	14·6 (87/594)
*<1	8·2 (52/635)	15·4 (99/642)	0·0001	0·49 (0·34–0·69)	11·8 (151/1277)

n = no of patients.
NS = not significant.

TABLE VI—MORTALITY BY AGE AND SEX

—	SK % (deaths/n)	C % (deaths/n)	p	RR (95% CI)	Total % (deaths/n)
Age (yr)					
≤65	5·7 (217/3824)	7·7 (291/3784)	0·0005	0·72 (0·60–0·87)	6·7 (508/7608)
>65–75	16·6 (240/1444)	18·1 (261/1442)	NS	0·90 (0·74–1·09)	17·4 (501/2886)
>75	28·9 (171/592)	33·1 (206/623)	NS	0·82 (0·64–1·05)	31·0 (377/1215)
Sex					
F	18·5 (214/1157)	22·6 (261/1156)	0·01	0·78 (0·64–0·95)	20·5 (475/2313)
M	8·8 (414/4703)	10·6 (497/4695)	0·004	0·82 (0·71–0·94)	9·7 (911/9398)

TABLE VII—MORTALITY BY SITE OF INFARCT AND BY PREVIOUS INFARCT

—	SK % (deaths/n)	C % (deaths/n)	p	RR (95% CI)	Total % (deaths/n)
Site of infarct					
Anterior	14·5 (309/2134)	18·4 (403/2193)	0·0006	0·75 (0·64–0·88)	16·5 (712/4327)
Inferior	6·8 (137/2009)	7·2 (145/2004)	NS	0·94 (0·74–1·20)	7·0 (282/4013)
Lateral	10·0 (30/300)	8·4 (21/251)	NS	1·22 (0·68–2·18)	9·3 (51/551)
Multiple location	9·0 (75/832)	13·9 (113/811)	0·002	0·61 (0·45–0·83)	11·4 (188/1643)
ST depression	20·5 (46/224)	16·3 (37/227)	NS	1·33 (0·82–2·14)	18·4 (83/451)
Undefined	8·0 (26/325)	8·6 (29/336)	NS	0·92 (0·53–1·60)	8·3 (55/661)
Previous infarct					
No	9·5 (468/4905)	12·3 (606/4926)	0·00001	0·75 (0·66–0·85)	10·9 (1074/9831)
Yes	16·9 (157/927)	16·5 (147/889)	NS	1·03 (0·80–1·32)	16·7 (304/1816)
Doubtful	14·3 (3/21)	16·7 (5/30)	NS	0·83 (0·17–4·00)	15·7 (8/51)

TABLE VIII—MORTALITY BY KILLIP SCALE

Grade	SK % (deaths/n)	C % (deaths/n)	p	RR (95% CI)	Total % (deaths/n)
1	5·9 (246/4171)	7·3 (298/4105)	0·01	0·80 (0·67–0·95)	6·6 (544/8276)
2	16·1 (215/1332)	19·9 (266/1340)	0·01	0·78 (0·64–0·95)	18·0 (481/2672)
3	33·0 (63/191)	39·0 (96/246)	NS	0·77 (0·52–1·14)	36·4 (159/437)
4	69·9 (102/146)	70·1 (94/134)	NS	0·99 (0·59–1·65)	70·0 (196/280)

TABLE IX—ADVERSE REACTIONS (AR) TO STREPTOKINASE TREATMENT (5860 PATIENTS)

	AR leading to withdrawal of SK infusion		AR attributed to SK after completion of infusion	
	No	%	No	%
Minor bleeds	30	0·5	188	3·2
Major bleeds	0	—	19	0·3
Allergic reactions	99	1·6	42	0·7
Anaphylactic shock	7	0·1	0	—
Hypotension	96	1·6	82	1·4
Shivering and fever	21	0·4	41	0·7
Ventricular arrhythmias	0	—	70	1·2
Stroke	0	—	10	0·2
	253	4·2	452	7·7

TABLE X—NON-FATAL MAJOR CLINICAL EVENTS IN HOSPITAL

Events	SK n=5860	C n=5852	% total n=11 712
Reinfarction	238	124	3·0
Pericarditis	382	705	9·3
Post-infarction angina	995	950	16·6
Left ventricular failure	752	875	13·9
Ventricular fibrillation	388	439	7·1
III° atrioventricular block	294	333	5·3
Asystole*	133	92	1·9
Pulmonary and systemic thromboembolism	29	64	0·8

*Sinoatrial block lasting more than 5 s.

that the positive effect of SK may be restricted to patients without previous infarcts.

The beneficial effect of SK did not differ in the low-risk groups of the Killip scale (table VIII) and in class 3 the numbers may have been too small for significant differences to emerge; only in class 4, the high-risk group, was the benefit clearly absent. The risk profile of SK treatment is summarised in table IX. The two most feared events, major bleeds (defined as need for transfusion of at least 2 units of blood) and anaphylactic shock (documentation of which was required in ad-hoc forms) proved to have a low incidence. The adverse reactions are reported according to whether they occurred during the SK infusion and led to suspension of the treatment, or after completion of the infusion. Assignment to either category was left to the clinician; and, since the trial was unblinded, these incidences are probably overestimated. Cerebrovascular events (defined as the sum of ischaemic and haemorrhagic episodes) in the SK and control groups have been examined blindly by an ad-hoc committee and will be the subject of a separate report. Suffice it to say that their incidence was very low (below 1%) and comparable in the two groups. The distribution of clinically relevant events recorded in the CCU and post-CCU periods for SK and C patients is shown in table X, which documents the previously observed higher incidence of reinfarction episodes and the lower incidence of clinically diagnosed pericarditis in SK-treated patients.[5,6]

Discussion

A large population was required to demonstrate, with reliable statistical power, the decrease of mortality of around 20% that was judged a clinically valuable benefit to be expected from intravenous thrombolysis. This was achieved by adoption of a protocol that gave a combination of formally controlled design, unequivocal end-points, and a simple operational setting[7] that closely resembled routine clinical practice.[8,9] As shown in table III, only 13·1% (4160/31 826) of patients routinely admitted to CCUs should have contra-indications while an active policy aimed at promoting earlier referral should decrease the numbers excluded because of arrival more than 12 h after onset, nearly one-third of the patients (10 257/31 826) in this trial. The results documented in fig 2 and in tables IV and V hardly require comment. Intravenous infusion of 1·5 million units of SK over 45–60 min produced a significant decrease in the overall mortality of the randomised population; although the benefit was most

striking in patients treated within 3 h from the onset of pain, it remained statistically significant also in the group treated between 3 and 6 h. A non-statistically significant reduction of mortality in favour of SK-treated patients is seen in the 6 to 9 h groups; this difference is reversed in the 9 to 12 h group but the numerators and the denominators here are very small, thus producing unstable estimates. A data-generated analysis of the 1277 patients randomised within 1 h after onset of pain suggests that very early treatment reduces in-hospital mortality by about 47%.

The second most important and complementary piece of information has to do with the safety profile of intravenous SK. The incidence of major and minor complications that have accompanied and followed the treatment seems largely acceptable (table IX).[10,11] It should be noted that no specific prophylactic treatment with steroids was included in the protocol nor was it practised by many of the participating centres.

According to the study protocol, the use of anticoagulant drugs was left to the decision of the individual clinical groups, who applied their standard regimens whether or not the patient received SK. A detailed analysis of the various treatment schemes will be provided elsewhere, but the results presented here must be seen as supporting the hypothesis that the beneficial effect is causally associated with SK only. The question remains open whether any form of anticoagulation could have improved the benefit, despite a possible increase in haemorrhagic complications. The specific role of anticoagulation (intravenous heparin, followed by oral anticoagulants or subcutaneous low-dose heparin) in preventing reocclusion of opened infarct-related arteries, and the contribution of reocclusion to mortality, need to be assessed in studies designed for this purpose, in the light of results with recombinant plasminogen activator in fully anticoagulated patients.[12,13]

Some indication of the patient characteristics that are associated with a greater beneficial effect of SK may be had from subgroup analyses: even though these can be regarded only as hypothesis generators, they deserve attention because of the large numbers on which they are based. Infarcts related to the territory served by the anterior descending coronary artery seem to have the best chance from intravenous thrombolysis (table VII). The difference in favour of SK treatment found in the large subgroup with inferior localisation should perhaps be further explored by other studies and with other thrombolytic treatments. Our results confirm, on larger numbers, the suggestions of other studies in which infarct site was considered.[6,14] There is no obvious reason why there should be such a clear-cut difference with SK in favour of the group of patients without a previous infarct.

The concentration of the beneficial effect of SK in the age-group below 65 years is consistent with the notion that thrombolysis should be more effective when the coronary bed is mechanically less hampered by atherosclerotic processes.[15] On the other hand, since a statistically non-significant positive effect was seen also in older age-groups and no specific adverse reactions or negative clinical events were recorded in this population, SK treatment cannot be seen as contraindicated in elderly infarct patients. Our large population sample allowed, for the first time, an adequate examination of the sex variable: although the well-known overall higher mortality of the female population was confirmed, the beneficial effect of SK treatment did not seem to differ substantially between the sexes.

Conclusions

In view of the high consistency of our findings with those obtained in smaller, more rigidly controlled studies,[5,6] intravenous infusion of 1·5 million units of SK can be recommended as a safe treatment for all patients with no positive contraindications who can be treated within 6 h from onset of pain. Retrospective pooled analyses[10] suggest that the period of benefit may be longer, and this possibility is still being tested in a major study.[16]

While the results of the follow-up are obviously of the greatest importance to provide the complete benefit profile of SK treatment, we suggest that the striking decrease of in-hospital mortality must be regarded as a valuable result on its own. It means that substantially more patients can live to receive further pharmacological and other treatments already known or suspected to improve the outcome after myocardial infarction.

The study would not have been possible without the active collaboration of the many nurses and doctors of all the participating CCUs.* The CCU nurses of Niguarda "De Gasperis" provided the night randomisation. The "A. Bianchi Bonomi" Haemophilia and Thrombosis Centre was available for consultation in cases of haemostatic complications.

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Participating centres continued at foot of next page

SMALL UPPER AIRWAY IN NEAR-MISS SUDDEN INFANT DEATH SYNDROME INFANTS AND THEIR FAMILIES

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Summary 6 infants (index cases) from five different families had a near-miss sudden infant death syndrome event between 3 and 12 weeks of age and had polygraphically documented apnoeas during sleep. 4 of their siblings had died of SIDS. The index cases, their 4 living siblings, 10 parents, and 8 grandparents underwent respiratory studies during sleep. All the adults and 3 index cases had cephalometric X-rays. 2 index cases underwent volume computerised tomographic scans when awake and during sleep. Index cases had mixed and obstructive sleep apnoea. Several family members had obstructive sleep apnoea; cephalometric X-rays also showed small upper airways, particularly behind the base of the tongue. A small posterior airway at the level of the tongue may be a familial risk factor for apnoea of infancy.

Introduction

THERE is speculation about a relation between the sleep apnoea observed in infants classified as "near-miss sudden infant death syndrome" (SIDS)[1-2] and the obstructive sleep apnoea syndrome in adults. We have described[3] 5 infants with apnoea during sleep who continued to have sleep-related breathing problems after 12 months of age leading to a typical obstructive sleep apnoea syndrome between 2 and 4 years of age. We did not investigate the mechanisms responsible for the breathing abnormalities during sleep then, but we have since done so in five families in which several members of variable age had obstructive sleep apnoea.

Subjects and Methods

Index Subjects

The index subjects were 6 infants from five families referred for unexplained apnoea. All had been found to be apnoeic when they were thought to be asleep, and all required vigorous resuscitation. They were admitted to hospital but the cause of the apnoea could not be identified. At the time the subjects were aged 3 to 12 weeks. All had been born normally at term and had been well up to the apnoeic episode. All underwent polygraphic study during sleep while they were in hospital.

Families of Index Cases

22 individuals who had family ties with the 6 index cases were investigated (fig 1).

Siblings.—4 siblings had died and had been diagnosed as SIDS after the necropsy, which had been done by a coroner, not by a specialist research team. There were 4 living siblings, none of whom had ever been diagnosed as "near-miss SIDS". Parents in family A, however, reported that their first son had had cyanosis and apnoea during sleep in early infancy. The living siblings' ages ranged from 6 weeks to 7 years when first seen.

GISSI PARTICIPATING CENTRES—*continued*

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