Outcome of very premature infants with necrotising enterocolitis cared for in centres with or without on site surgical facilities

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Abstract

***Objective*—To determine if the presence of a neonatal surgical facility on site has any effect on mortality and morbidity of very premature infants with necrotising enterocolitis (NEC).**

***Design and Setting*—Retrospective review of infants of less than 29 weeks gestation cared for in the seven perinatal centres in New South Wales.**

***Patients*—Between 1992 and 1997, 605 infants were cared for in two centres with in house surgical facilities (group 1) and 1195 in five centres where transfers were required for surgical management (group 2).**

***Results*—Although use of antenatal steroids was significantly lower in group 1 centres than group 2 centres (74% *v* 85% respectively), and the incidence of hyaline membrane disease, pneumothorax, and NEC was higher, mortality was identical (27%). Fifty two (9%) infants in group 1 and 72 (6%) in group 2 of comparable perinatal characteristics and CRIB (Clinical Risk Index for Babies) scores developed radiologically or pathologically proven NEC. The overall mortality of infants with NEC in group 1 was lower but this was not statistically significant (27% *v* 35%). Significantly more infants with NEC in group 1 had surgery (69% *v* 39%). There were fewer postoperative deaths in group 1 and more deaths without surgery in group 2. The duration of respiratory and nutritional support and hospital stay for the survivors were similar in the two groups. In a multivariate analysis, shorter gestation was the only factor associated with mortality in infants with NEC; the presence of in house surgical facilities was not.**

***Conclusions*—There were no significant differences in outcome of premature infants with NEC managed in perinatal centres with or without on site surgical facilities. Early transfers should be encouraged. This finding may have implications for future planning of facilities for neonatal care.**

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Keywords: necrotising enterocolitis; premature infants; transfer; mortality

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Necrotising enterocolitis (NEC) is the commonest surgical emergency encountered in the neonatal period.[1 2] Most cases are found in premature infants, with incidence and mortality rising with decreasing gestation and birth weight.[3–5] Although many cases of NEC can be successfully managed medically, 30–60% ultimately require surgery.[1–3 6–8] The improved survival of surgically treated infants with NEC of all gestational ages, currently more than 70%,[2 7 8] has been attributed to improved surgical and nursing expertise and experience in centres equipped for neonatal surgery.

However, not all neonatal intensive care units (NICUs) have in house surgical facilities. Current opinion recommends a modest caseload to maintain expertise.[9] Thus infants with NEC who need surgical care are transferred to a centralised neonatal surgical tertiary unit. Transport of any ill preterm infant can be problematic, with instability caused by handling having adverse effects on outcome.[10] Bowman *et al*[11] showed increased mortality in premature infants transferred between tertiary perinatal centres, but others did not agree.[12] When, if at all, to transfer and operate on an ill infant with NEC is less clear. The potential risks of transfer have to be weighed against the surgical needs of the infant.[13]

The aim of this study was to compare the mortality and morbidity of very premature infants with NEC managed in centres with on site surgical facilities with similar infants in centres where transfer for surgery is necessary. The hypothesis is that management of such infants in surgical tertiary centres without the need of transport or a change in management team is associated with a better overall outcome.

Patients and methods

New South Wales (NSW) has seven tertiary perinatal centres providing neonatal intensive care. During most of the study period (1992–1997 inclusively), two centres had surgical facilities on site, one of which ceased to have in house surgical facilities from October 1995. Neonates needing surgical intervention were transported to either of the two above centres or to the neonatal facilities of the two children's hospitals for further management. All centres are university affiliated hospitals and have subspecialty trained neonatologists in attendance full time. All centres without surgical facilities, except one, have visiting paediatric surgeons from the two children's hospitals for consultation. Neonatal transport was conducted by either of the specialised teams from the two children's hospitals, and the services were

Table 1 Comparison of all 1800 infants cared for in centres with on site surgical facilities (group 1) or in centres without (group 2)

Variable	*Group 1*	*Group 2*	*p Value*	*Odds ratio (95% CI)*
No of infants	605	1195		
Gestation (weeks)	26.3 (1.4)	26.4 (1.4)	0.15	
Birth weight (g)	919 (231)	929 (226)	0.38	
Male sex	318 (53%)	613 (51%)	0.62	1.05 (0.86 to 1.28)
Pre-eclampsia	82 (14%)	175 (15%)	0.57	0.91 (0.69 to 1.21)
Antepartum haemorrhage	180 (30%)	357 (30%)	1.00	0.99 (0.80 to 1.23)
Growth restriction	34 (6%)	67 (6%)	1.00	1.00 (0.66 to 1.53)
Antenatal corticosteroid	449 (74%)	1016 (85%)	<0.0001*	0.51 (0.40 to 0.65)
Apgar at 5 min	7.0 (1.8)	7.1 (1.8)	0.27	
HMD	483 (80%)	862 (72%)	0.0004*	1.53 (1.21 to 1.94)
Surfactant treatment	362 (60%)	754 (63%)	0.18	0.87 (0.71 to 1.07)
Pneumothorax	85 (14%)	120 (10%)	0.02*	1.46 (1.09 to 1.97)
Proven NEC	52 (9%)	72 (6%)	0.048*	1.47 (1.01 to 2.13)
IVH (grade 3–4)	61 (10%)	128 (11%)	0.75	0.94 (0.68 to 1.29)
Death	162 (27%)	324 (27%)	0.91	0.98 (0.79 to 1.23)
Steroid for CLD	205 (34%)	434 (36%)	0.32	0.90 (0.73 to 1.10)
ROP (grade 3–4)	85 (14%)	19 (9%)	0.002*	1.63 (1.20 to 2.20)
Ventilation (days)	15.0 (17.5)	17.7 (20.0)	0.003*	
Oxygen (days)	47.1 (49.0)	40.4 (45.6)	0.005*	
TPN (days)	14.1 (16.9)	13.9 (14.0)	0.80	
Hospital stay (days)	59.5 (49.4)	61.5 (44.6)	0.40	

Values are mean (SD) or number (%).
*p<0.05.
HMD, Hyaline membrane disease; NEC, necrotising enterocolitis; IVH, intraventricular haemorrhage; CLD, chronic lung disease; ROP, retinopathy of prematurity; TPN, total parenteral nutrition.

amalgamated to a single statewide service in 1995.[14]

Between January 1992 and December 1997, all premature infants born at less than 29 weeks gestation and cared for in these seven centres were included in the study. The audit officer of each unit entered information pertaining to his or her care into the NSW Neonatal Intensive Care Unit Study (NICUS) database. Using this database, we searched for all premature infants of less than 29 weeks gestation with proven NEC cared for in either one of the two types of centre. Information collected from the NICUS database was compared with and supplemented by review of all inpatient hospital records of infants with NEC. Infants cared for in centres with in house surgical facilities (group 1) and infants in centres without these facilities (group 2) were compared.

Proven NEC was defined in the NICUS database as radiological evidence of pneumatosis intestinalis (with or without perforation) and/or pathologically proven NEC at surgery or post mortem. Infants with only clinically suspected NEC, without radiological or pathological evidence, were not included in the study.

Data examined included perinatal risk factors such as gestational age, birth weight, maternal history, birth history, and the Clinical Risk Index for Babies (CRIB) score[15]. Illnesses concurrent with or before the onset of NEC, the feeding history, age of onset of NEC, severity of NEC as suggested by abnormal haematological variables, and the need for assisted ventilation and pressor support during the 10 days after NEC onset were also noted.[16]

Outcomes compared included mortality from NEC, frequency of surgery, duration of ventilation, supplemental oxygen, total parenteral nutrition, and hospital stay. Fisher's exact test and parametric and non-parametric analyses where appropriate were used for group variable comparisons, and multivariate analysis was used for risk adjustments. The Statistical Package for Social Science (SPSS) PC version 9.0 was used for statistical analysis.

Results

Of the 1800 preterm infants born at less than 29 weeks gestation during the study period, 605 were cared for in centres with surgical facilities on site and 1195 in centres without surgical facilities. The infant population and hospital outcome were similar in the two groups of centres. The two populations of infants were similar in terms of frequency of antenatal problems and they had similar mean gestational ages and birth weights (table 1). However, infants born at surgical perinatal centres received antenatal steroids less often than similar infants in non-surgical centres (74.2% *v* 85%; $p < 0.0001$). These infants had a higher incidence of hyaline membrane disease (HMD) (79.8% *v* 72.1%; $p = 0.0004$) and pulmonary air leak (14% *v* 10%, $p = 0.015$). The incidence of proven NEC was significantly higher among infants in group 1 (9% *v* 6%, $p = 0.048$). In spite of these differences, the overall hospital mortality was identical (27%). On average, infants in group 1 spent less time receiving positive pressure ventilation ($p = 0.003$), but more time in supplemental oxygen ($p = 0.005$). Severe grades of retinopathy of prematurity (ROP) were more common among infants in group 1 ($p = 0.002$), but not severe intraventricular haemorrhage (IVH grade 3 or 4) or chronic lung disease (CLD) requiring treatment with postnatal steroids.

A total of 128 premature infants with a discharge diagnosis of proven NEC were reviewed. Four infants (two from each group) were excluded from this study for the following reasons. One was diagnosed as having haematochezia, but had no radiological evidence of NEC. Three other infants, on close scrutiny of medical records, had insufficient clinical evidence of NEC and no evidence of pneumatosis intestinalis radiologically. All four infants survived. The remaining 124 infants were included in the study.

The incidence of NEC in this infant population of less than 29 weeks gestation was thus 6.9%. The mean (SD) gestation and birth weight were 26.2 (1.4) weeks and 894 (231) g respectively. Fifty two infants with NEC were cared for in the two tertiary centres with surgical facilities (group 1), and the remaining 72 were cared for in centres where transfer for surgery was required (group 2). Table 2 summarises the perinatal characteristics. The CRIB scores were similar in the two groups of infants. The use of antenatal steroids was lower in infants in group 1, but this difference did not reach significance (71% *v* 86%, $p = 0.07$). The incidence of air leaks was higher in infants in group 1 (21.2% *v* 4.2%, $p = 0.004$), but the incidence of HMD, use of surfactant, and treatment of patent ductus arteriosus were similar for the two groups.

Table 3 summarises clinical variables relating to NEC and its outcome in the two groups of premature infants. Most of the infants in both groups were fed before the onset of NEC.

Table 2 Comparison of early perinatal characteristics in infants with necrotising enterocolitis cared for in centres with on site surgical facilities (group 1) and in centres without (group 2)

Variable	*Group 1*	*Group 2*	*p Value*	*Odds ratio (95% CI)*
No of infants	52	72		
Gestation (weeks)	26.2 (1.3)	26.2 (1.4)	1.00	
Birth weight (g)	887 (241)	889 (225)	0.96	
Male sex	26 (50%)	40 (55%)	0.80	0.59 (0.39 to 1.64)
Pre-eclampsia	6 (12%)	6 (8%)	0.77	1.21 (0.38 to 3.84)
Antepartum haemorrhage	19 (37%)	18 (25%)	0.23	1.73 (0.79 to 3.76)
Growth restriction	6 (12%)	6 (8%)	0.56	1.44 (0.44 to 4.73)
Antenatal corticosteroids	37 (71%)	62 (86%)	0.07	0.40 (0.23 to 1.08)
Apgar at 5 min	7.0 (1.7)	7.2 (1.7)	0.52	
CRIB score	5.9 (3.7)	5.8 (4.0)	0.89	
HMD	39 (75%)	59 (82%)	0.38	0.66 (0.28 to 1.58)
Surfactant treatment	31 (60%)	45 (63%)	0.85	0.89 (0.43 to 1.84)
Pneumothorax	11 (21%)	3 (4%)	0.004*	6.17 (1.63 to 23.43)
Indomethacin for PDA	20 (39%)	19 (26%)	0.17	1.74 (0.81 to 3.75)
PDA surgery	7 (14%)	4 (6%)	0.20	2.64 (0.73 to 9.56)
IVH (grade 3–4)	3 (6%)	8 (11%)	0.36	0.49 (0.12 to 1.94)

Values are mean (SD) or number (%).
*p<0.05.
HMD, hyaline membrane disease; PDA, patent ductus arteriosus; IVH, intraventricular haemorrhage.

The age at first feed and NEC onset were similar between the groups. The rates of blood culture positive septicaemia in association with NEC were similar. On comparing haematological indices for severity of NEC, the lowest platelet count was lower in group 1 than group 2 infants (114×10^9 *v* 188×10^9/l respectively, p = 0.02). The lowest neutrophil count during NEC was, however, lower in group 2 infants (8.0×10^9 *v* 4.4×10^9/l, p = 0.01). The two groups of infants had similar rates of mechanical ventilation and correction of acidosis with intravenous bicarbonate as a result of NEC, but the infants in group 1 received inotropic support more often (59% *v* 32%, p = 0.01).

The overall mortality was not significantly different between the two groups (27% in group 1 infants and 35% in group 2) and averaged 31.5% for the whole population. Thirty eight of the 52 infants in group 1 had subsequent resection for intestinal stricture. A further two had stricture resection after initially successful medical management. Fourteen infants died, 11 after surgery during acute NEC and three without surgery. Thirty four (47%) of the 72 infants in group 2 were transferred to surgical centres. Not all transferred infants had surgery: six did not and one of them died. Of the 28 infants who had surgery, 13 died after the operation. One surgically treated survivor needed further resection for intestinal stricture. Of the 38 infants in group 2 who were not transferred, 10 died. The overall rate of surgery for NEC was significantly higher among infants in group 1 (73% *v* 39%, p = 0.0002). Group 1 infants showed a trend towards a lower mortality after surgery, and more group 2 infants died without surgery (table 3). The duration of supplemental oxygen, mechanical ventilation, total parenteral nutrition, and hospital stay were similar for the survivors in the two groups.

Table 3 Comparison of clinical course and outcome of infants with necrotising enterocolitis (NEC) cared for in centres with on site surgical facilities (group 1) and in centres without (group 2)

Variables	*Group 1 (n=52)*	*Group 2 (n=72)*	*p Value*	*Odds ratio (95% CI)*
NEC clinical course				
Age at onset of NEC (days)	23.3 (13.6)	25.7 (17.0)	0.39	
Fed before NEC	47 (90%)	65 (90%)	1.00	1.01 (0.30 to 3.39)
Age at first feed (days)	7.0 (4.7)	7.4 (5.2)	0.66	
Proven sepsis with NEC	16 (31%)	25 (35%)	0.70	0.84 (0.39 to 1.79)
Lowest platelet ($\times 10^9$/l)	114 (98)	176 (188)	0.02*	
Lowest WCC ($\times 10^9$/l)	8.0 (9.1)	4.4 (4.9)	0.01*	
Ventilated for NEC	49 (94%)	63 (88%)	0.36	2.33 (0.60 to 9.08)
Inotropes for NEC	29 (56%)	23 (32%)	0.01*	2.69 (1.28 to 5.62)
Bicarbonate for acidosis	7 (14%)	13 (18%)	0.62	0.71 (0.26 to 1.91)
Acute NEC surgery	36 (69%)	28 (39%)	0.001*	3.53 (1.66 to 7.53)
Deaths	14/52 (27%)	25/72 (35%)	0.43	0.69 (0.32 to 1.51)
Died after acute surgery	11/36 (31%)	14/28 (50%)	0.13	0.44 (0.16 to 1.22)
Died w/o surgery	3/52 (6%)	11/72 (17%)	0.15	0.34 (0.09 to 1.28)
Survivors	38	47		
Resection for stricture	3 (8%)	1 (2%)	0.32	3.94 (0.39 to 39.5)
CLD at 36 weeks	15/38 (39%)	21/47 (45%)	0.66	0.80 (0.34 to 1.92)
Steroid for CLD	18/38 (47%)	30/47 (63%)	0.19	0.51 (0.21 to 1.22)
Ventilation (days)	27.4 (16.7)	33.5 (28.1)	0.22	
Oxygen (days)	58.8 (32)	61.3 (58.4)	0.80	
ROP (grade 3–4)	9/38 (24%)	8/47 (17%)	0.58	1.51 (0.52 to 4.40)
TPN (days)	37 (21)	32.6 (20.3)	0.33	
Hospital stay (days)	93.9 (30.2)	97.6 (47.7)	0.67	

Values are mean (SD) or number (%).
*p<0.05.
WCC, White blood cell count; CLD, chronic lung disease; ROP, retinopathy of prematurity; TPN, total parenteral nutrition.

Multivariate analysis using backward stepwise logistic regression based on likelihood ratio was performed for the 124 infants with NEC. Variables entered were gestation, birth weight, CRIB score, antenatal steroids, HMD, and group designation, with death as the outcome variable. Gestation was the only significant variable after elimination steps. The final model was constructed with three variables: gestation with antenatal steroid and group designation as forced entries. Gestation appeared to be the only independent factor that was close to statistical significance (odds ratio (OR) 0.77 per week increment, 95% confidence interval (95% CI) 0.57 to 1.04). Neither antenatal steroids (OR 1.39, 95% CI 0.50 to 3.84) nor the centre of care (group 2: OR 1.33, 95% CI 0.51 to 3.10) affected mortality independently.

Discussion

This study is the first population study to compare outcomes in management of NEC in premature infants between tertiary perinatal centres with surgical facilities and those without. It also seeks to establish the possible effects of transport on outcomes in ill premature infants with NEC. The incidence of NEC at 6.9% in this premature population is comparable to that of other studies.[2–5] However, the average age of NEC onset of 25 days was higher than in previous series.[2 5] This is probably related to the short gestation of our study population.[3 4]

We found that the overall infant population was similar in the two groups of perinatal centres, and the neonatal outcomes were comparable. Most of the important variables that affect mortality, such as gestational age, birth weight, and CRIB score, were well matched in the infants with NEC in the two groups of perinatal centres, but a few differences were present as a result of individual centre circumstances or practices. These differences were not confined to infants with NEC but were representative of the respective infant populations. The most notable difference was the lower use of antenatal steroids in infants in

group 1. This could account for the larger number of infants with HMD and pneumothorax in this group. The use of antenatal steroids may decrease the chances of developing NEC in infants at risk, and our findings that infants in group 2 had a lower incidence of NEC are consistent with those of Halac and colleagues.[17] Whether this has a bearing on the severity of NEC and its effect on mortality is not known. However, when use of antenatal steroids was added to the multivariate analysis, it was found not to affect mortality in this NEC cohort.

In general, the characteristics of NEC at onset were similar in the two groups of infants in terms of postnatal age, feeding before NEC, and the need for supportive medical treatment. Infants in group 1 had a higher rate of inotropic support and surgical intervention. This may reflect greater severity of NEC in these infants or individual practice variation. NEC surgery at a rate of 73% is high, but our population is more premature than in other studies.[3 4 7 8] Infants in group 1 had lower platelet counts. This may have been due to the higher incidence of surgery. Those in group 2 had lower leucocyte counts and more died without surgery. This may also reflect the fact that not having neonatal surgical facilities on hand may influence the decision for transfer of infants with critical NEC for surgery, aggressive medical management being used instead. When and how to operate on a neonate with NEC is still the subject of much discussion,[16] even more so if there is a lack of surgical facilities on site. Primary peritoneal drainage is only an adjunct to resuscitation and usually requires the skills of a surgeon, because a lack of response within 24 hours must still lead to operative laparotomy.[6] More infants with NEC in surgical centres had surgery during the acute phase, and this was not offset by subsequent surgery for strictures in the infants from non-surgical centres. This observation may be explained by the fact that surgeons have a lower threshold for surgery than referring neonatologists in non-surgical centres. Despite a trend towards lower mortality after surgery in surgically equipped perinatal centres, the overall mortality was not significantly different. For survivors of NEC, the duration of subsequent respiratory and parenteral nutritional support in intensive care was similar in the two groups.

The delivery of babies with antenatally diagnosed surgical problems should probably be arranged to be in surgical perinatal centres or colocated obstetric and children's hospitals. However, NEC is a common surgical problem that arises suddenly and quickly in premature infants in the neonatal period. Although the possible complications of interhospital transfer of ill children have been emphasised,[9] the risk of transferring such infants between level III centres is not clear.[11 12 18] Our findings contrast with those of Bowman and colleagues.[11] The transfer of premature infants with NEC, whether they subsequently had surgery or not, did not increase the overall mortality in group 2 infants. Harding and Morton[12] felt that perinatal outcomes depend more on the centre of care than the possible adverse effects of transfer. Our study showed that the group of centres, whether or not they needed to transfer to surgical facilities, did not independently influence mortality. In fact, decreasing gestational age was the only factor seen to affect mortality. This is consistent with the findings of other studies.[3 5]

The NICUs in our population study are all tertiary centres. It was recently shown that mortality in Australian NICUs was lower than in Scottish units. This was attributed to better medical and nursing staffing.[19] In NSW, this is further supplemented with a specialised retrieval service.[14] Our efficient perinatal services may account for the lack of differences in the mortality and morbidity examined. Planners of perinatal facilities have to ask whether it is safer and more cost effective to transfer infants with NEC to surgical centres or plan to have surgical facilities brought to such infants at risk on site. Our results show that there is no significant difference in NEC outcomes between the two models of care in NSW.

On the other hand, infants cared for in centres with surgical facilities had a non-significant trend towards lower overall mortality (27% *v* 35%) despite receiving less antenatal steroids and having a higher incidence of NEC. It is possible that statistical significance would be found with a larger sample size. Ten infants who were not transferred and one who was transferred died without surgery, in contrast with only three infants in surgical centres who died without surgery. The infants who were not transferred may have been judged to be too ill for transfer and may have survived if surgical facilities were on site. Half of the transferred infants who had surgery died. Therefore, it is also possible that infants became more unstable and ill after the transfer leading to a trend to higher postoperative mortality.

However, the trend toward lower mortality may not be practically manifest if future planning were to include surgical facilities for all tertiary perinatal centres or even to have a "mobile" surgical team to perform the operation. The concern in balancing harm and benefit is that such decentralisation of specialist surgical services would dilute clinical experience to the point where any benefits would be offset. Specialist paediatric services also depend on other specialties for support such as paediatric radiology, paediatric anaesthesia, pathology, and specialist nursing. All these require the concentration of expertise and facilities for optimal training of the duty medical and nursing staff, development of support services, and ultimately better results.[9] The availability of a specialised paediatric emergency transport service would also support the benefits of centralisation. One could recommend that these very premature infants with NEC be transferred as early as practical. This approach is justified because of the high mortality and need for surgical intervention.

Important questions remain about the long term growth and developmental outcome of the survivors, which were not examined in this comparative study. Our previous study[20] from a

centre with on site surgical facilities has emphasised the need for long term follow up. Increased neurodevelopment morbidity was shown in infants with NEC who required surgery compared with gestation matched controls without NEC and medically treated infants with NEC. Therefore, a further study to compare long term outcome in these two models of care is required.

In conclusion, we find that management of premature infants with NEC in perinatal centres where transfer is required for surgery is not significantly associated with increased mortality. We also find that management of premature infants with NEC in perinatal centres with surgical facilities on site is not necessarily associated with a better outcome. This is reassuring for the current model of neonatal care and transfer in NSW, and may help influence planning of perinatal facilities in the future.

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