Cause of death and making end-of-life decisions in preterm infants has not changed over time: a mortality follow-back survey

Linde Goossens[1], Laure Dombrecht[2,3], Kenneth Chambaere[2,3], Kim Beernaert[2,3], Filip Cools[4]

[1] Department of Neonatal Intensive Care, Ghent University Hospital, Belgium

[2] End-of-Life Care Research Group, Ghent University & Vrije Universiteit Brussel (VUB), Belgium

[3] Department of Public Health and Primary Care, Ghent University, Belgium

[4] Department of Neonatal Intensive Care, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Belgium

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Corresponding author: Linde Goossens, Department of Neonatal Intensive Care, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent. Tel +32 9 332 35 39. Email: linde.goossens@uzgent.be

Abstract

Aim

This study aimed to evaluate changes over time in cause of death and making end-of-life decisions in preterm infants.

Methods

A follow-back survey was conducted of all preterm infants who died between September 2016 and December 2017 in Flanders and Brussels, Belgium. Cause of death was obtained from the death certificate and information on end-of-life decisions (ELDs) through an anonymous questionnaire of the certifying physician. Results were compared with a previous study performed between August 1999 and July 2000.

Results

In the cohort 1999-2000 and 2016-2017 respectively, 150 and 135 deaths were included. A significantly higher proportion of infants born before 26 weeks of gestation was found in the 2016-2017 cohort (53% versus 24% in 1999-2000, $p<0.001$). Extreme immaturity (<26 weeks) remained the most prevalent cause with a significant increase in 2016-2017 (48% versus 28% in 1999-2000, $p<0.001$). The overall prevalence of ELDs was similar across study periods (61%). Non-treatment decisions remained the most common ELD (36% and 37%).

Conclusion

Infants born at the limits of viability have become more prevalent among infant deaths, possibly due to a change in attitude towards periviable births. Neither the process of making ELDs, nor the cause of death has changed over time.

Keywords

end-of-life decisions, cause of death, preterm infants

Key Notes

- Information regarding cause of death and end-of-life decisions in preterm infants is scarce.
- Although the proportion of infants born at the limits of viability has become more prevalent among infant deaths, the process of making end-of-life decisions and the cause of death has not changed over time.
- Systematic and transparent population-based research is necessary in the future to further improve the quality of end-of-life care in neonates.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Abbreviations

ELD: end-of-life decision

NTD: non-treatment decision

SIDS: sudden infant death syndrome

1 Introduction

Worldwide between 6.8 to 13.2 % of children are born prematurely, that is before 37 weeks of gestation.[1] The global average preterm birth rate in 2020 was estimated to be 9.9%. Preterm birth is an important cause of death in early life.[2] In a population-based mortality study in 2016-2017 in Flanders, Belgium, 64% of all deaths under the age of one year were prematurely born infants and 55% of the deaths occurred in the first week of life.[3] When comparing the 2016-2017 cohort with a similar Flemish cohort of deaths from 1999-2000,[4] infants born at less than 26 weeks of gestation have become a more important contributor representing 34% of all deaths in 2016-2017 versus 14% in 1999-2000.

As many neonatal deaths can be anticipated, they are often preceded by an end-of-life decision.[5] Neonatal end-of-life decisions (ELDs) include non-treatment decisions such as withholding or withdrawing potentially life-prolonging treatment, or administering pain and/or symptom relief medication, with a potential or explicit life-shortening effect. In Flanders, 76% of all non-sudden deaths under the age of one year were accompanied by at least one ELD. Of those ELDs, 60% were non-treatment decisions, and in 40% a drug was administered to alleviate pain and/or symptoms with accompanying possible or explicit life-shortening intention.[3]

Even though preterm infants make up a large part of early childhood deaths, population-based mortality studies have never focused on this population to describe the circumstances of, and the medical decisions made at the end-of-life. Moreover, due to both, a shift in the clinical profile of this preterm population with significantly more extreme preterm infants, as well as important changes in neonatal care, it can be assumed that these circumstances and decisions have considerably changed over the past two decades. Examples of significant changes in neonatal care are the ongoing technological advancements but most of all the introduction of new quality improvement policies, such as review of outcome data using continuous quality improvement methods.[6] These days, infants who are born at the limits of viability are increasingly offered life-saving care.[7,8] Despite their improved chance for survival, they remain highly susceptible to severe complications compromising

their future.[9,10] Therefore, neonatal care teams are increasingly confronted with ethical dilemmas about the best treatment options when taking care of these extremely vulnerable infants. Also, it is generally accepted that parental involvement in medical discussions regarding the care of their child is essential.[11] This means decisions to redirect life-saving care towards comfort care are now shared decisions taken together with the parents, as any other medical decision. Whether these changes have had an impact on how neonatal care teams make end-of-life decisions in preterm infants, is not known.

In order to further improve perinatal palliative care in this vulnerable population of preterm infants, documenting the underlying causes and circumstances of death are necessary. This population-based study aimed to explore shifts in end-of-life decision-making in the population of deceased preterm infants in Flanders, Belgium, over the past two decades and whether these changes could be related to the cause of death.

2 Patients and Methods

2.1 Study design, setting and participants

This study carried out an in dept-analysis of the population of preterm infants, being part of a broader population-level mortality follow-back survey performed in 2016-2017 in Flanders, Belgium, including all deaths of children under the age of one year. We focused our analysis on the group of infants born at less than 37 weeks of gestation residing in Flanders and Brussels, who died between September 2016 and December 2017. Questionnaires were sent to the certifying physician. All cases were identified through the death certificates signed within the inclusion period.[3] A similar study in Flanders and Brussels had been done previously between August 1999 and July 2000.[4] The design of both study periods was identical. A mortality follow-back procedure was followed, slightly modifying well-established procedures in adults[12] and minors.[13] Details of the study protocol have been published separately.[14] STROBE guidelines for reporting cross sectional research were followed.

2.2 Data collection

Within four months after death, the certifying physician received a questionnaire by post through the Flemish Agency for Care and Health who is responsible for processing the death certificates. Anonymity of the child, parents and physician was ensured by procedures involving a lawyer as intermediary between death certificate authorities, physicians and researchers.

2.3 Questionnaires and variables

The same demographic and clinical patient data such as place of death, sex, age at death, gestational age at birth and cause of death, were obtained from the death certificates in 2016-2017 as in 1999-2000. Using a deterministic linkage procedure, data from the death certificates was linked to questionnaire data. We used small cells analysis to ensure that reidentification based on the linked database was prevented.

Based on death certificates of all live-born preterm infants who died in Flanders and Brussels in 1999-2000 and 2016-2017, the leading cause of death was identified. In accordance with WHO definitions, early neonatal mortality was defined as death under the age of seven days after birth (day of birth is day zero), and late neonatal mortality was defined as death between seven and 27 days after live birth.

Classification into six cause-specific death categories was made, taking into account clinically relevant common features. The process of classification was founded on the principles of the International Classification of Diseases 10^{th} revision and discussed with an expert panel including two neonatologists, both senior staff members. The formed categories were comparable with most death categories described in international studies. It should be noted that the primary cause of death was established by the Flemish Agency for Care and Health who is responsible for processing the information, written on the death certificate by the treating physician at the time of death. Therefore, primary causes of death could not be altered by, nor discussed with, the principal investigator. Cause of death categories were defined as follows: death due to extreme immaturity and maternal related conditions, death due to cardiopulmonary diseases, death due to gastrointestinal complications, death due to central nervous system injuries, death due to congenital

disorders and death due to other disorders (Table 1). Infants whose cause of death was classified as other, died of a variety of diseases with a different pathophysiological origin. Therefore this group could not be characterized by a single common cause.

Information on ELDs was obtained from the validated questionnaires of the post-mortem population survey. The first question asked whether death had been sudden and unexpected. If not, an ELD was considered possible and physicians were asked whether any ELD preceded the death. If so, whether they had made a non-treatment decision,withholding or withdrawing treatment, or if the end-of-life decision implied the use of medication, with or without life-shortening intention.

2.4 Statistical analysis

Results were analysed using IBM SPSS statistics for Macintosh, version 28.0, released in 2021 (Armonk, New York, United States). Chi-square tests, two-tailed Fisher's exact tests and Kruskal Wallis tests were used to compare changes over time in the socio-demographic and clinical characteristics, the different types of ELDs comparing the two study periods , and the type of ELD in correlation with the cause-specific death category. A two-sided p value of less than 0.05 was considered to indicate statistical significance. When significant, a post hoc pairwise comparison analysis was performed using z-tests, applying a Bonferroni correction.

2.5 Ethical approval

Ethical approval for the population-level mortality follow-back survey was obtained from the Ethics Committee of Ghent University (B670201628795), the Privacy Commission (SA3/VT005071970), and the National Council of the Order of Physicians (BD/wc/89997) and the Sectoral Committee of Social Security and Health (SCSZG/16/234). This study was supported by all eight Flemish neonatal intensive care units.

3 Results

The mortality follow-back survey had a response rate of 253/292 in 1999-2000 (87%) and 229/276 in 2016-2017 (83%). No significant difference in demographic characteristics between deaths with and without a response was found for both survey periods. Therefore weighting of results was not

deemed necessary.[3] The study included a total number of 150 premature infants in 1999-2000 and 135 premature infants in 2016-2017, who were born alive in Flanders and Brussels and died under the age of one year.

Statistically significant differences between both study periods were found for gestational age (Table 1). The proportion of deceased infants born at less than 26 weeks of gestation was higher in 2016-2017 (24.0% versus 53.3% respectively; p value <0.001) whereas the number of deceased infant born between 32 and 36 weeks of gestation was significantly lower (38.0% versus 18.5% respectively; p value <0.001). With regard to sex and timing of death (<seven days, between seven-27 days, >27 days), no significant change was observed.

In both study periods, extreme immaturity and maternal conditions (28.0% and 48.1% in 1999-2000 and 2016-2017, respectively) followed by congenital malformations (24.0% and 16.3% in 1999-2000 and 2016-2017, respectively), remained the most prevalent causes of death. However a significant increase (p value <0.001) was observed between both study periods in the proportion of children who died as a consequence of extreme immaturity and maternal conditions.

We found a similar prevalence of ELDs in this population of preterm infants across study periods: 60.7% in 1999-2000 versus 61.5% in 2016-2017 (Table 2). Non-treatment decisions (NTDs) were the most common ELD, representing 37.3% and 36.3% of the ELDs made in both periods, respectively. Withdrawal of ventilatory support was the most frequently applied NTD (81.8%). The use of medication with hastening death taken into account was noted in 15.3% and 12.6% respectively, and with an explicit life-shortening intention in 8.0% and 12.6% of all deaths in preterm infants, respectively. Although a slight increase was observed in the use of drugs with an explicit intention to hasten death in 2016-2017, the difference was not statistically significant (p=0.241) (Table 2). The different types of NTDs in 2016-2017 are summarised in Table 3.

In 2016-2017, morphine and other opioids could be identified as the most frequently used drugs in pain and symptom management, with possible life-shortening intention, at the end of life (30 cases

representing 88.2% of all infants receiving drugs), followed by benzodiazepines (11 cases representing 32.4%) (Table 4). Neuromuscular blocking agents were used in 5 patients (14.7%). Comparison of the 2 study periods within a same death category, showed no statistically significant difference in whether or not and which end-of-life decisions were made (table not shown because of small numbers). Formal statistical analyses of trends over time concerning the type of ELD in relation to the death category, were not possible due to small cell counts. However, looking at the trends, the NTD remained the most common ELD throughout both cohorts.

4 Discussion

Changes in ELDs and cause-specific mortality in preterm infants over time had not been described in a Belgian population. This survey identified the circumstances and most prevalent causes of death in preterm infants in Flanders, based on the information provided on the death certificate. Comparing two time periods,1999-2000 and 2016-2017, small but non-significant changes in death causes over time were noted. In the study period 2016-2017 a significantly higher number of infants born before 26 weeks of gestation were registered and consequently a significantly higher number of premature born infants died as a result of extreme immaturity and maternal conditions around birth. The type of ELD in the cohort 2016-2017 did not significantly differ from the 1999-2000 cohort between death causes.

In the two time periods studied, extreme immaturity and maternal conditions were the most prevalent causes of neonatal mortality in preterm infants, listed on the death certificate. This finding is consistent with previous studies in other high-income countries.[15] The observation of a relative decrease in deaths attributable to pulmonary causes, has been reported by several other authors and may be explained by changes in neonatal care such as the prenatal use of glucocorticoids and antibiotic agents, the use of surfactant and the development of new ventilation strategies. [16] The remarkable drop in the category other from 10.7% in 1999-2000 to 2.2% in 2016-2017 could be attributed to significantly fewer cases of sudden infant death syndrome (SIDS) over time.[17] In Belgium, as in many other countries, campaigns promoting the supine sleep position started during

the 1990s and were responsible for a decrease in SIDS mortality. Yet coding practices for SIDS have also changed over time due to recommendations for standardised investigations of all neonatal deaths, including autopsy.[18] Therefore a number of previously unknown causes of mortality were now diagnosed and will be no longer classified as SIDS, as SIDS remains a diagnosis of exclusion.[19] Whereas 10 babies in total were diagnosed with SIDS in 1999-2000 , there were none in 2016-2017. Continuous improvement in perinatal and neonatal intensive care and an increasing trend towards active treatment for infants born at the limits of viability, have resulted in an improved survival rate of extremely preterm infants.[16,20] These infants, however, remain at high risk of neonatal mortality. This could explain the significant increase in the proportion of infants that died before 26 weeks of gestation in the cohort 2016-2017. The number of births before 26 weeks of gestation has not significantly changed over the last two decades in Flanders, but since intensive care was not common practice at the time of the first cohort, it is plausible that a number of these children were classified as stillborn. The number of deceased infants born between 32 and 36 weeks of gestation on the other hand, was significantly lower in 2016-2017. We hypothesise that most likely the development of new techniques and increasing knowledge are responsible for the increase in the number of survivors.

End-of-life decisions are an integral part of medical practice in critically ill neonates in Flanders.[21] In concordance with previous studies, NTD with parental involvement made up the largest proportion of end-of-life decisions and appear to have become more acceptable than 20 years ago.[15,22] Consistent with findings in international literature, withdrawal of ventilatory support was also in our study the most common NTD.[23] Another possible, but more controversial NTD, is the withdrawal of artificial nutrition and hydration. Although nutrition is often considered as the basis of child care and a pillar of parenthood, the American Academy of Pediatrics described the withdrawal of artificial nutrition as legitimate when it is part of a palliative care program.[24] Withdrawal of artificial feeding can cause stress for parents and may induce the perception that their child died from starvation and not from the initial disease.[25] However, the mail goal should be to reduce discomfort in the baby. At

any time, the decision to withdraw artificial nutrition and hydration should be individualised, taking into account that the benefits for the baby should outweigh the burdens. Little is known about the type of medication and the doses that are used in neonates in the context of palliative care. Appropriate pain and/or symptom alleviation by means of medication is considered good clinical practice. Consistent with findings from international research, opioids are the drugs most frequently given during end-of-life care among infants under the age of one year.[26,27] Even though the use of lethal (doses of) drugs in neonates is illegal in Belgium,because Belgium's euthanasia law only includes adults and competent minors, medication administered with an explicit intention to hasten death was reported in both study periods. In the majority of these cases increasing doses of sedatives and opioids were administered. This confirms previous findings from scarce international literature.[26,27] The life-shortening effect of non-lethal drugs, used to treat pain and symptoms at the end of life, is an inevitable side-effect that is generally accepted. Assuming that the palliative medication use is proportionate and given to relieve the suffering of neonates for whom there was no hope of a bearable future or any chance of survival. This is also known as the rule of double effect.[28]. It is reassuring that, in contrast with the cohort 1999-2000 where the use of potassium chloride was registered in 3 cases, there were none in the cohort 2016-2017. Potassium chloride has no indication whatsoever in comfort care in neonates. An open debate about drug-related hastening of death in neonates could contribute to an increased quality of palliative care and may reduce the moral burden in caregivers, faced with the inevitable death of a newborn.

4.1 Strengths and limitations

This population-based, follow-back survey had a high response rate of 87% in 1999-2000 and 83% in 2016-2017, providing a number of infants representing the total population of deceased newborns in Belgium. A full-population survey has the additional advantage of collecting a wide range of data which allows generalisability for a specific population. Also, the design of the study was based on reliable, well-established procedures and previously validated questionnaires on end-of-life decisions in neonates, minors and adults.[4,13,12] Some strengths can be attributed to the death certificate

method in particular. Such as international comparability, lack of patient burden and consequent attrition rates, anonymity, and exclusion of possible selection bias by selecting certain physicians for the study.[12]

This study had some limitations. The primary cause of death was derived from the death certificate but not adjusted with the information obtained from medical records, which would have been more accurate.[29] Therefore the distinction between causation and co-occurrence of a disease leading to death is not always evident. A suboptimal classification of death may have occurred due to the retrospective design of the study. Our categorisation attempted to capture a logical, system-based approach, verified by an expert panel. Due to small numbers, intrinsic to the chosen study population, formal statistical analyses were not always possible. On the other hand, because our study population can be considered as representative for the whole group of deceased preterm infants in Belgium, even non-statistically significant results can be acknowledged as true shifts over years.

5. Conclusion

We found an increased prevalence of extreme prematurity, i.e. birth before 26 weeks of gestation, over time in a population-based preterm infant death cohort in Flanders and Brussels. Extreme immaturity and related maternal conditions, followed by congenital malformations remain the most prevalent death causes. Neonatal death in preterm infants is often preceded by an end-of-life decision with the potential or certain effect of hastening death. Non-treatment decisions remain the most common type of ELD. No distinct type of ELD, NTD or the use of drugs, could be related to a specific death category in the study period 2016-2017. In a minority of cases drugs were given with the explicit intention to hasten death.

Systematic and transparent population-based research to monitor death causes and evaluate the process of making ELDs-is necessary in the future to further improve the quality of end-of-life care in neonates. As end-of-life care in infants should be considered equally important as life-saving care.

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Table 1

		1999-2000		**2016-2017**		**P value**
		12 months		16 months		
		N	%	N	%	
Gestational age at birth: less than 37 weeks		150		135		
Sex						0.806
	Male	96	64.0	84	62.2	
	Female	54	36.0	51	37.8	
Gestational age						<0.001
	<26 weeks	36	24.0	72	53.3	
	26-28 weeks	38	25.3	28	20.7	
	29-31 weeks	19	12.7	10	7.4	
	32-36 weeks	57	38.0	25	18.5	
Age at death						0.227
	less than 7 days	93	62.0	86	63.7	
	7-27 days	22	14.7	27	20.0	
	more than 27 days	35	23.3	22	16.3	
Cause of death						<0.001
	Extreme immaturity & Maternal conditions	42	28.0	65	48.1	
	Cardio-Pulmonary	24	16.0	13	9.6	
	Gastrointestinal, Necrotising enterocolitis, Sepsis/Infection	21	14.0	13	9.6	
	Neurological, (peripartal) Asphyxia, Intraventricular hemorrhage	11	7.3	19	14.1	
	Congenital disorders	36	24.0	22	16.3	
	Other	16	10.7	3	2.2	

Table 1: Characteristics of deaths before one year of age of prematurely born children in Flanders, cohort 1999-2000 versus cohort 2016-2017

Table 2

	1999-2000 (12 months)		2016-2017 (16 months)		P value[a]
	N	%	N	%	
No ELD possible (death entirely sudden and unexpected)	26	17.3	20	14.8	0.630
ELD possible, but not made (death non-sudden)	33	22.0	32	23.7	0.778
ELD made	91	60.7	83	61.5	0.904
Non-treatment decision	56	37.3	49	36.3	0.902
Withholding treatment	23	15.3	19	14.1	0.867
Withdrawing treatment	33	22.0	30	22.2	1.000
Use of drugs	35	23.3	34	25.2	0.782
Medication with hastening death taken into account	23	15.3	17	12.6	0.609
Medication with an explicit intention to hasten death	12	8.0	17	12.6	0.241

When more than one ELD was noted by physicians, only the most important decision was used. The most important decision is the decision with the most explicit life-shortening intention. When more than one ELD with the same life-shortening intention was noted, administration of drugs (active) prevailed over withholding or withdrawing treatment (passive).

[a] Fisher's exact test: independent variable = study period, dependent variable = ELD type present yes/no.

Table 2: ELDs taken in deaths before one year of age of prematurely born children in Flanders, cohort 1999-2000 versus cohort 2016-2017

Table 3

	N	%
Antibiotics	9	20.5
Other medication, with exception of antibiotics	16	36.4
Fluid	8	18.2
Enteral feeding	7	15.9
Ventilation	36	81.8
Reanimation	23	52.3
Surgical procedure	3	6.8
Other	3	6.8

Table 3: types of Non-Treatment Decisions taken in preterm infants in Flanders: cohort 2016-2017 (indicating therapies that were withheld or withdrawn – no data available for 1999-2000)

Table 4

	N	%
Barbiturate	3	8.8
Benzodiazepine	11	32.4
Morphine and other opioid medicin	30	88.2
Neuromuscular blocking agent	5	14.7
Potassium chloride	0	0.0
Other	1	2.9

Table 4: types of drugs used in the context of palliative care in preterm infants in Flanders: cohort 2016-2017
(administration of potassium chloride was included because it used to be administered in a few cases at the end stage of palliative care in the past)