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Early and late operation of cleft lip and intelligence quotient and psychosocial development in 3–7 years

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ABSTRACT

Background: Early and late operations of the cleft lip represent exposure to general anesthesia during the first year of life. The early exposure to the anesthetics may influence long term neurological outcome. Timing of the operation may also influence the quality of life as babies with early repair might be accepted better by their families.
Aims: The aim of the study was to compare outcomes between two groups of patients operated on for the cleft lip in the first year of life.
Study design: Observational cohort study.
Subjects: Early repair group included patients operated on in the first eight days of life and late repair group those operated on between 3 and 10 months.
Outcome measures: Intelligence quotient (IQ) and psychosocial development of children who were operated on for cleft lip were compared at the age of 3–7 years.
Results: No differences were found between early (n = 15) and late (n = 17) repair group in terms of IQ. In both IQ was within the normal range: 100.00 (SD 13.867), 98.76 (SD 10.109), respectively. Significantly better results in physical functioning (P = 0.042) and self-esteem (P = 0.014) concepts in early repair group were found.
Conclusions: We compared outcomes of two groups of patients operated on for cleft lip in the first year of life. The earlier anesthesia did not show a negative impact on intelligence quotient in 3–7 years compared to later anesthesia. The earlier repair of the cleft lip showed a significant positive impact on psychosocial development in 2 out of 13 concepts tested.

1. Introduction

Recent experimental and clinical studies have suggested an association between early anesthetic exposure and late cognitive impairment. The existence of a "window of vulnerability" for the human brain and the proper timing of anesthesia is an ongoing question. Anesthetic agents work at the level of the synapse. Many of them antagonize the NMDA (N-methyl-D-aspartate glutamate) receptor or stimulate the GABA (gamma-aminobutyric acid) system or both. The toxic effect of anesthesia is most evident during stages of life when synaptogenesis is at its greatest [1]. Several animal studies suggest that anesthetic drugs cause histopathologic changes in the developing brains of animals [2–4]. The first studies performed on rodents showed a clear window of immature brain vulnerability within the first days of life [5]. Further studies on rhesus monkeys also identified the vulnerability window within the first week of life. While administration of anesthetic agents on day 5 caused demonstrable neuronal loss, administration on day 35 did not [6]. Within the "window of vulnerability", the earlier exposure to anesthetics is supposed to cause potentially greater impairment [6,7].

In humans, there is a possible association between the early exposure to the anesthetics and the late neurodevelopment impairment [8]. The vulnerability period for anesthetic-induced neurotoxicity might be up to 3 years of age [9,10]. Larger studies on human neonates focusing on the influence of anesthetic exposure early in life on later cognitive development are lacking [7]. Several studies support the theory of neurocognitive impairment in children after anesthesia [1,3,11],

Abbreviations: NMDA, N-methyl-D-aspartate glutamate; GABA, gamma-aminobutyric acid; IQ, intelligence quotient; SON-R, Hogrefe/Snijders-Oomen Non-Verbal Intelligence Test — Revised; CHQ 50, The Child Health Questionnaire 50; SD, standard deviation

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while others do not confirm this hypothesis [12,13]. The risk of neurotoxocity and neurodegeneration after exposure of human neonates to anesthetic agents should be considered before any surgery. Specific considerations such as patient age, duration, type and dose of anesthesia would be the most important factors for long term neurological outcome [10]. Currently, there is no study available which focuses on timing of general anesthesia in children within the vulnerability period for anesthetic-induced neurotoxicity and neurocognitive outcome.

Majority of patients with cleft lip are operated on during the first year of life. Early operation (within the first week of life) has several advantages: better wound healing, better cosmetic outcome, and less complications. The early operation of the cleft lip may also influence the quality of life as babies with early repair might be accepted better by their families [14,15]. The possible disadvantage may be the negative effect of early general anesthesia on the developing brain. There are no available data that focused on neurocognitive outcomes and quality of life of patients after early and late surgeries for cleft lip.

The aim of our study was to compare intelligence quotient (IQ) and quality of life between two groups of patients operated on for the same diagnosis (isolated cleft lip). The first group was operated on within the first 8 days of life while the second group between 3 and 10 months.

2. Material and methods

2.1. Patients

Patients in the first group (early repair) were operated on in the first 8 days of life while patients in the second group (late repair) were operated on between 3 and 10 months of life. The outcomes evaluated were IQ and psychosocial development assessed at three to seven years with SON-R (Hogrefe/Snijders-Oomen Non-Verbal Intelligence Test — Revised) and CHQ 50 (The Child Health Questionnaire 50) tests.

The patients included in this study were born between 2004 and 2008 in the Czech Republic and with a cleft lip. The Department of Plastic Surgery at the University Hospital Kralovske Vinohrady is a specialized center for cleft anomalies repair in patients from the Czech Republic. Information from their register was used to identify the groups. Until 2006 primary lip closure was performed at 3–10 months of age. In 2006 a program for early surgery started in the Czech Republic with an increasing number of patients being operated on during the first week of life. In 2007 early surgery became the gold standard with almost all patients operated on within the first week of life. This new therapeutic strategy was developed due to new evidence and understanding of the fetal wound healing process ensuring a better cosmetic outcome [14,15].

The inclusion criteria for patients in our study were: babies born in the Czech Republic between 2004 and 2008 with an isolated cleft lip (without cleft palate) who underwent primary lip closure under general anesthesia. The exclusion criteria were: more than one anesthetic exposure during life, birth weight less than 2000 g, gestational age less than 36 + 0 weeks and signs of perinatal asphyxia (defined as the need for resuscitation after delivery or Apgar scores <5 at 5 min and <7 at 10 min). The study was approved by the institutional ethics committee. Patients were enrolled in the study after informed consent from their parents had been obtained.

2.2. Anesthesia

In all patients the same protocol of general anesthesia was followed. Table 1 summarizes general anesthesia protocol used in all patients.

Table 1
Anesthesia protocol used in all patients included in the study.

Anesthesia protocol	
Analgesia	Sufentanil infusion starting 30 min before intubation Dose: 0.5–1 microgram/kg/h, discontinued after intubation
Endotracheal intubation	All patients before operation
Induction to general anesthesia	Sevoflurane, concentration 4–5%
Maintenance of general anesthesia	Sevoflurane, concentration 1–3%
Additional analgesia	None

2.3. Tests

All children were examined during the study period (May–October 2012) at the age of 3–7 years by one clinical psychologist specializing in pediatric neuropsychology (RH) using the SON-R 2.5–7 years test and the CHQ 50 test. The clinical psychologist did not have information about the timing of the operations and did not know if the patients were from the early or late repair group.

The SON-R 2.5–7 years (Hogrefe/Snijders-Oomen Non-Verbal Intelligence Test — Revised) is a test used to measure general intelligence in children validated in the Czech Republic for the actual age groups. The test is suitable for all children between the ages of 2.5 and 7 years. The test is non-verbal. The fact that written or spoken language is not required during testing makes the test particularly suitable for children with language or verbal communication difficulties that children with cleft lip often have. SON-R for the age range 2.5–7 years comprises six different sub-tests: Mosaics, Categories, Puzzles, Analogies, Situations and Patterns.

The sub-tests can be grouped into two types: reasoning tests (Categories, Analogies and Situations) and spatial performance tests (Mosaics, Puzzles and Patterns). The performance tests are so called because the item is solved while manipulating the test stimuli. In the reasoning tests the correct solution is chosen from a number of given alternatives. However, perceptual, spatial and reasoning abilities play a role in all of the sub-tests. The test duration is approximately 50 min. The test software evaluates results according to the child's age. The main outcome is the intelligence quotient (IQ) with a normal range of 85–115 [16–18].

In both groups parents completed the CHQ 50 test (The Child Health Questionnaire 50). CHQ 50 is a general quality of life survey validated in the Czech Republic for the actual age groups. The test measures unique physical and psychosocial concepts: physical functioning, role (social–emotional), role (social–physical), bodily pain, general behavior, mental health, self-esteem, general health, change of health, parental emotional impact, parental time impact, family activities and family cohesion. This method yields a profile for each of the health concepts. The higher the score is for each parameter in the evaluated age group the higher the health state measured [19,20]. Minimum and maximum possible values for each concept are listed in Table 3.

2.4. Statistics

Data are presented as mean and SD (standard deviation). BMDP Statistical software (Dickson WJ, Chief Editor, University of California Press, Los Angeles, USA, 1990) was used for statistical analysis. The Mann–Whitney non-parametric test and parametric *t*-test were used when indicated. All statistical tests are based on a significance level of $P < 0.05$.

3. Results

The total sample of 46 children born with cleft lip between 2004 and 2008 in the Czech Republic and fulfilling the study criteria was found in the register. Among those were 21 children operated on early in life (early repair group) and 25 children operated on later in life (late repair group). From the early repair group, four patients did not attend the examination and a further two were excluded as during testing we found that they experienced more than one anesthesia. The final sample