PAIN® 155 (2014) 2368–2376

www.elsevier.com/locate/pain

Noxious stimulation in children receiving general anaesthesia evokes an increase in delta frequency brain activity

Caroline Hartley [a,1], Ravi Poorun [b,1], Sezgi Goksan [b], Alan Worley [c], Stewart Boyd [c], Richard Rogers [d], Tariq Ali [d], Rebeccah Slater [a,*]

[a] Department of Paediatrics, University of Oxford, Oxford, UK
[b] Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[c] Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children, London, UK
[d] Nuffield Department of Anaesthesia, John Radcliffe Hospital, Oxford, UK

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 14 July 2014
Received in revised form 22 August 2014
Accepted 3 September 2014

Keywords:
EEG
Anaesthetics
Paediatrics

ABSTRACT

More than 235,000 children/year in the UK receive general anaesthesia, but it is unknown whether nociceptive stimuli alter cortical brain activity in anaesthetised children. Time-locked electroencephalogram (EEG) responses to experimental tactile stimuli, experimental noxious stimuli, and clinically required cannulation were examined in 51 children (ages 1–12 years) under sevoflurane monoanaesthesia. Based on a pilot study (n = 12), we hypothesised that noxious stimulation in children receiving sevoflurane monoanaesthesia would evoke an increase in delta activity. This was tested in an independent sample of children (n = 39), where a subset (n = 11) had topical local anaesthetic applied prior to stimulation. A novel method of time-locking the stimuli to the EEG recording was developed using an event detection interface and high-speed camera. Clinical cannulation evoked a significant increase (34.2 ± 8.3%) in delta activity ($P = 0.042$), without concomitant changes in heart rate or reflex withdrawal, which was not observed when local anaesthetic was applied ($P = 0.30$). Experimental tactile ($P = 0.012$) and noxious ($P = 0.0099$) stimulation also evoked significant increases in delta activity, but the magnitude of the response was graded with stimulus intensity, with the greatest increase evoked by cannulation. We demonstrate that experimental and clinically essential noxious procedures, undertaken in anaesthetised children, alter the pattern of EEG activity, that this response can be inhibited by local anaesthetic, and that this measure is more sensitive than other physiological indicators of nociception. This technique provides the possibility that sensitivity to noxious stimuli during anaesthesia could be investigated in other clinical populations.

1. Introduction

The prevention of pain is one of the primary goals of anaesthesia during surgical procedures. While it is clear in both adults and children that anaesthesia can supress autonomic and motor responses following noxious stimuli, it is not known whether abolition of these measures equates to the provision of adequate analgesia [5]. Indeed, the concept of balanced anaesthesia [19] is based on our understanding that different compounds can independently affect analgesia, muscle relaxation, reduction or elimination of autonomic reflexes, and amnesia.

Cerebral cortical processing is a fundamental component of pain perception [33]. In nonverbal populations, measures of cortical activity may provide the best insight into whether an individual is in pain, and in the case of the anaesthetised patient, whether the anaesthetic provision is antinociceptive. In adults, recent investigations report that noxious stimuli administered during anaesthesia alter electroencephalography (EEG) activity. While many studies, in both animals [23,24] and adult patients [3,12,16,21,31], report an increase in delta activity, a smaller number of studies also report the opposite finding [2,12,17,31]. The observation that noxious stimulation in anaesthetised adults can lead to both increased and decreased delta activity has been attributed to the different

* Corresponding author at: Department of Paediatrics, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK. Tel.: +44 1865 234229.
E-mail address: rebeccah.slater@paediatrics.ox.ac.uk (R. Slater).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.pain.2014.09.006
0304-3959/

doses and types of anaesthetics used in these studies, and to the different surgical procedures under investigation [2,3,26,31]. As delta activity is the dominant pattern of brain activity in anaesthetised subjects, how this activity is modulated by external events, such as nociceptive stimulation, is important in understanding how the brain processes information when patients are in an unresponsive state.

In the UK, more than 235,000 children admitted to hospital each year receive an operation or investigation under general anaesthesia [9]. To date, cortical responses to noxious stimuli have not been investigated in anaesthetised children. As the brain continually undergoes development throughout childhood and adolescence, it cannot be assumed that children will respond to noxious stimuli in the same way as adults when anaesthetised. In the first few years of life there is a rapid increase in myelination [25] and an increase in synaptic density, followed by a period of synaptic pruning until mid-adolescence [14]. These developmental changes are reflected in changes in EEG frequency [11] and synchrony [35], and grey and white matter volume [25]. Additionally, there is a relative lack of research into the effect of drugs on children, and their effects at different ages. Recording direct measures of neurophysiological brain activity in response to noxious stimulation has the potential to provide a more complete understanding of how nociceptive information is being processed in the anaesthetised child. A first step toward this goal is to characterise the electrophysiological brain response evoked by a controlled nociceptive stimulus in children who are receiving a fixed dose of a single anaesthetic agent.

Due to its wide therapeutic index and fast speed of induction, sevoflurane is the preferred agent for gaseous anaesthetic induction in children. The study aim was to establish whether tactile (innocuous) and noxious stimuli evoke changes in electrophysiological brain activity of children receiving sevoflurane monoanaesthesia. A novel method of time-locking the EEG to clinical and experimental procedures was developed. Based on the literature in adults [3,12,16,21,31], which shows that noxious stimulation can evoke an increase in delta activity, and following a pilot study performed in 12 children, which showed results consistent with this observation, we hypothesised that noxious stimuli would cause an increase in delta activity. We aimed to test whether clinical cannulation and experimental innocuous and noxious stimuli evoked this response. In addition, we examined whether this increase in delta activity was blocked by the application of local anaesthetic.

2. Materials and methods

2.1. Subjects

Ethical approval was granted by the Oxford Research Ethics Committee of the National Research Ethics Service. Informed written parental consent and, where appropriate, the child's assent, were obtained prior to each study. The study conformed to the standards set by the Declaration of Helsinki and Good Clinical Practice guidelines.

Fifty-one children (number of males = 26) aged 1–12 years receiving an elective operation or investigative magnetic resonance imaging (MRI) scan under general anaesthesia were recruited from the John Radcliffe Children's Hospital, Oxford between July 2012 and February 2014 (see recruitment flow chart in Fig. 1). This age range was selected because an end-tidal concentration of 2.5% is equivalent to 1 minimum alveolar concentration of sevoflurane across this age [18]. Children were included in the study if a gaseous induction of anaesthesia was required. Examples of the procedures that the children required include MRI scans, squint repair, hernia repair, and orchidopexy. Children were not eligible for inclusion in the study if they received premedication before anaesthetic induction or if they required an intravenous anaesthetic induction. Participants requiring emergency care, having central nervous system disease or developmental delay, were also excluded.

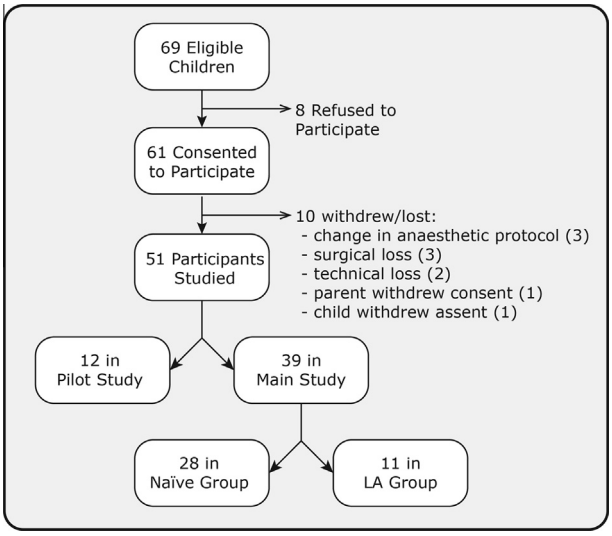

Fig. 1. Recruitment flow chart. LA, local anaesthetic.

Twelve children were included in the pilot study (age range: 19–143 months). In the main study, subjects were divided into 2 groups: 1) the naïve group (n = 28, age range: 14–153 months) and 2) the local anaesthetic (LA) group (n = 11, age range: 25–83 months) who had topical LA cream applied to the stimulus site.

2.2. Anaesthetic procedures

Gaseous induction of anaesthesia was performed following routine anaesthetic practice using sevoflurane (Baxter, Newbury, Berkshire, UK), oxygen, and nitrous oxide. Once stable, a laryngeal mask airway was inserted, nitrous oxide was turned off, and sevoflurane reduced, to achieve an end-tidal concentration of 2.5%. The patients were maintained under sevoflurane monoanaesthesia. The time between the induction of anaesthesia and starting the experimental stimuli was at least 10 minutes (the time for electrode placement), at which point end-tidal nitrous oxide levels were confirmed to be <5% and sevoflurane levels stabilised at an end-tidal concentration of 2.5%, equivalent to 1 minimum alveolar concentration (MAC) of sevoflurane across the participant age range [18]. No recordings were made until these levels were reached and anaesthesia was stable.

A subset of children (n = 11, age range: 28–100 months) had topical local anaesthetic (tetracaine 4% w/w – Ametop Gel; Smith and Nephew Healthcare, London, UK) applied to the dorsum of both hands at least 30 minutes prior to anaesthetic induction. The decision to apply local anaesthetic was made by nursing staff. If nursing staff were not informed by the anaesthetists that children were going to have a gaseous induction, then local anaesthetic was applied in case intravenous anaesthetic induction was required.

2.3. Experimental recording techniques

Electrodes were applied to the surface of the skin immediately after anaesthetic induction. Eight EEG recording electrodes (Ambu Neuroline disposable Ag/AgCl cup electrodes; Ambu, Ballerup, Denmark) were positioned on the scalp at Cz, CPz, C3, C4, Fz, FCz,