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Brainwave entrainment to minimise sedative drug doses in paediatric surgery: a randomised controlled trial

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Abstract

Background: Anaesthetic drugs may cause neuroapoptosis in children and are routinely used off-label in specific age groups. Techniques that reduce anaesthetic drug dose requirements in children may thus enhance the safety of paediatric sedation or anaesthesia. Brainwave entrainment, notably in the form of auditory binaural beats, has been shown to have sedative effects in adults. We evaluated the influence of brainwave entrainment on propofol dose requirements for sedation in children.

Methods: We randomised 49 boys scheduled for sub-umbilical surgery under caudal blockade to an entrainment or a control group. Small differences in pitch were applied to each ear to create binaural beats, supplemented by synchronous visual stimuli, within the electroencephalographic frequency bands seen during relaxation and (rapid eye movement/non-rapid eye movement) sleep. After establishment of caudal block, propofol infusion was started at 5 mg kg^{-1} h^{-1}. Intraoperatively, the infusion rate was adjusted every 5 min depending on the sedation state judged by the bispectral index (BIS). The infusion rate was decreased by 1 mg kg^{-1} h^{-1} if BIS was <70, and was increased if BIS was >70, heart rate increased by 20%, or if there were other signs of inadequate sedation.

Results: Mean propofol infusion rates were 3.0 (95% confidence interval [CI]: 2.4–3.6) mg kg^{-1} h^{-1} *vs* 4.2 (95% CI: 3.6–4.8) mg kg^{-1} h^{-1} in the entrainment and control groups, respectively ($P<0.01$). BIS values were similar in the two groups.

Conclusions: Brainwave entrainment effectively reduced the propofol infusion rates required for sedation in children undergoing surgery with regional anaesthesia. Further studies are needed to investigate the possibility of phasing out propofol infusions completely during longer surgical procedures and optimising the settings of brainwave stimulation.

Clinical trial registration: DRKS00005064.

Keywords: anaesthesia; caudal blockade; brainwave entrainment; children; conscious sedation; propofol

Editor's key points

- Tones of slightly different frequencies applied to the left and right ears of a subject generate a so-called binaural beat manifest as an increase in EEG power at the frequency difference between the applied tones.
- Binaural beats have been shown to have anxiolytic, sedative, and analgesic effects in adults.
- The authors performed a randomised trial of the influence of binaural beats on propofol requirements for sedation in children undergoing sub-umbilical surgery performed under caudal analgesia.
- Binaural beats significantly reduced propofol requirements.

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The use of general anaesthetics remains controversial in children.[1,2] There is ample evidence of neurodegenerative changes in developing rodents and monkeys after exposure to general anaesthetics,[3–6] with adverse implications for learning and behaviour.[7–11] Even in small children, several anaesthetic drugs have been linked to behavioural disorders and impaired cerebral development.[12,13]

A number of observational studies have also been published, albeit some of them with small effect sizes, in which procedures that required general anaesthesia were found to be associated with learning and behavioural deficits.[14–20] Moreover, most sedative and analgesic drugs continue to be used off-label in some paediatric age groups.[21] The only reasonable lesson to be drawn from these concerns is that any concepts that may help to reduce the perioperative dose requirements for sedative drugs in children should be regarded as potentially useful and conducive to the safety of paediatric anaesthesia.

One such concept is brainwave entrainment, a non-pharmacological method of sedation, notably in the form of binaural beats with addition of a visual stimulus. Binaural beats have been shown to be useful for relaxation, sedation, or reduction of pain and anxiety in adults.[22–24] They are generated inside the brain from the neural output of two separate tones being applied directly to each ear, with a small difference in pitch or frequency of each tone. A phase resonance is thus created, which will cause the brainwaves, in an attempt to locate the sound source, to pulsate 'in sync' with this frequency difference. In this way, the pitches can be adjusted, such that the frequency difference will fall into one of the encephalographic frequency bands known to be associated with specific states of brain activity ranging from excitement to deep sleep.

Despite an emerging interest amongst clinicians, no clinical data have yet been available on brainwave entrainment and its potential towards ensuring sedation and minimising requirements of general anaesthetics in paediatric surgery. We therefore designed an investigator-blinded and randomised controlled study into such entrainment as a means of lowering propofol requirements for sedation in children undergoing sub-umbilical surgery under caudal analgesia.

Methods

Preparations

We obtained approval of the study protocol from the institutional review board (ethics committee) at the Medical University of Vienna (ref. 1506/2012; date of approval: October 2012), and registered the study both with the Austrian Agency for Health and Food Safety (INS-621000-0401; date of approval: April 2013) and in the German Clinical Trials Register (DRKS-ID: DRKS00005064; date of approval: November 2014) before patient enrolment.

Patient enrolment

From September 2013 to May 2016, we considered 54 boys aged 1–6 yr who were scheduled for elective sub-umbilical procedures under caudal anaesthesia at the Division of Paediatric Surgery (Medical University of Vienna). All parents gave their written informed consent based on comprehensive information provided about the nature and scope of the study and the procedures to be conducted.

Exclusion criteria

Criteria resulting in exclusion from the study were deafness or impaired hearing; blindness; epilepsy or other neurological disorders requiring continuous hypnotic medication; contraindications to midazolam, propofol administration, or caudal blockade; history of brain injury, disability, or allergy; and inability to understand the study protocol or all procedures related to the study.

Randomisation and masking

After applying these exclusion criteria, 49 of these boys could be randomly assigned to a group receiving brainwave entrainment or to a control group, in which the entrainment device (MindLights®; Mindfield Biosystems, Gronau, Germany) was fitted over the patients' heads, but was not activated. Hence, the anaesthesiologists in charge were unable to see whether the device was on or off during the anaesthetic procedure.

Anaesthesia management

Our departmental standard of care requires preoperative fasting of 6 h for solid food, 4 h for breast milk, and 2 h for clear fluids. Midazolam 0.5 mg kg^{-1} was administered orally or rectally 30 min before the induction of anaesthesia, which was accomplished via a face mask administering a mixture of sevoflurane/oxygen/air. Sevoflurane administration was immediately stopped after establishment of venous access. A caudal block was performed under ultrasound guidance with ropivacaine 0.38% (1 ml kg^{-1} body weight). Haemodynamic monitoring included electrocardiography, noninvasive blood pressure, and peripheral oxygen saturation. Continuous infusion of propofol started out at 5 mg kg^{-1} body weight h^{-1}, and spontaneous ventilation was maintained throughout the anaesthetic procedure.

Brainwave entrainment

Figure 1 illustrates the clinical setting with the audiovisual entrainment device in place (MindLights; Mindfield Biosystems). The device was fitted 10 min after the onset of the caudal blockade, at the time of skin incision for the surgical procedure. The binaural beats applied in the study group commenced at a frequency difference of 10 Hz, were then reduced by 2 Hz every 150 s until the software setting was down to 2 Hz, and were finally maintained at a steady state oscillating between 1 and 2 Hz to keep the brain continuously stimulated. For visual stimulation, we selected sinus-shaped variation of light intensity with primary colours and synchronous phase variation.

Bispectral index monitoring

Sedation was assessed by means of continuous bispectral index (BIS) monitoring, via an electrode placed on the patient's carefully cleaned forehead, as per the manufacturer's instructions (Covidien/Medtronic, Boulder, CO, USA). After the skin incision, if the BIS was below 70, the propofol infusion rate was reduced by 1 mg kg^{-1} h^{-1} every 5 min. Conversely, the dose was increased whenever we noted a BIS value exceeding 70, any other sign of inadequate sedation such as spontaneous movement, or an increase in heart rate of more than 20%.

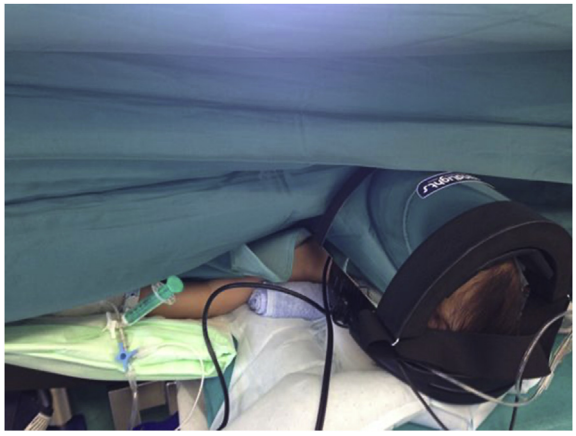

Fig 1. Clinical setting with the brainwave entrainment device fitted over a patient's head. The device featured a light-emitting diode mask and headphones connected to a laptop computer and oxygen supply.

Study hypothesis and outcome parameter

As null hypothesis, we postulated that the propofol requirements to maintain sedation would not differ between both groups, the alternative hypothesis being that such a difference would be demonstrable. Accordingly, the primary outcome parameter of this study were the dose requirements for continuous propofol infusion (in mg kg^{-1} body weight h^{-1}) to maintain BIS values between 60 and 70.

Power and statistical analysis

Our sample size estimates were aimed at disclosing the dose concentration of propofol needed to achieve BIS values of 65 in children aged 1 yr or over. They resulted in a sample size of 23 per group to detect a clinically meaningful difference of 30% (5 [2] mg kg^{-1} h^{-1} as within-group standard deviation) at a power of 80%, given an alpha level of 0.05. To make allowances for any dropouts, we increased this sample size to 27 per group. Propofol dose, duration of surgery, age, and weight were evaluated by means of an independent Student's *t*-test or a Mann–Whitney *U*-test, as appropriate. Differences with *P*-values <0.05 were considered statistically significant.

Results

No adverse events, whether related or unrelated to the investigation, were observed throughout the study. Table 1 lists a pertinent selection of patient data and Fig 2 a study flow chart as required by the Consolidated Standards of Reporting Trials system for transparent trial reporting.

The mean dose requirement to maintain sedation was 3.0 mg kg^{-1} h^{-1} in the entrainment group (95% confidence interval [CI]: 2.4–3.6) as compared with 4.2 mg kg^{-1} h^{-1} in the control group (95% CI: 3.6–4.8). Hence, the null hypothesis for the primary outcome parameter was rejected, as the intraoperative requirements for propofol were indeed found to differ significantly in both groups (P=0.013).

Table 1 Characteristics of children having received or not received brainwave entrainment in the present study, expressed as absolute or mean values (range or standard deviation)

	Entrainment (n=23)	Control (n=26)
Age (yr)	3 (1–6)	3 (1–6)
Weight (kg)	15.6 (4.3)	14.5 (4.1)
Duration of surgery (min)	58.3 (36.7)	48.5 (27.6)
Duration of anaesthesia (min)	69.4 (38.6)	59.9 (30.7)

The mean differences between intraoperative and preoperative BIS values were 5.98 (95% CI: 2.17–9.79) for the control group and 4.35 (95% CI: 1.28–7.41) for the entrainment group (P=0.51 for the difference between the groups).

Discussion

This is the first communication to report clinical results of brainwave entrainment aimed at minimising dose requirements of propofol for effective sedation of children during surgical procedures. We used this novel approach in the setting of sub-umbilical surgery under caudal blockade and achieved dose reductions that were statistically significant. Hence, our findings indicate that brainwave entrainment can effectively reduce the use of anaesthetic drugs in the scenario of paediatric surgery.

Non-pharmacological means of sedation are particularly useful in children. Concerns arise from the fact that virtually none of the available general anaesthetics are labelled for all paediatric age groups, but also from ongoing discussions about general anaesthetics promoting neuronal apoptosis in children.[5,6,25] There is preclinical evidence of these drugs bringing about changes in the developing brain[26,27] that are linked to long-term learning and behavioural deficits.[9,10] Observational studies have succeeded in translating these findings from animal models to humans by associating repeated exposure to procedures that require general anaesthesia with deficits in learning, behaviour, fine motor coordination, and general intelligence.[1,20]

The effectiveness of binaural beats has been addressed in many studies dealing with conditions, such as anxiety,[28] tinnitus,[29] myofascial pain syndrome,[30] or attention-deficit/hyperactivity disorder.[31] Pertinent research is also available into preoperative anxiety of adult patients in day-case surgery.[22] The phenomenon of brainwave entrainment (i.e. of brainwaves synchronising with auditory, visual, or tactile input) can be traced on electroencephalograms based on four bands of cerebral activity. Beta is the highest-frequency band, ranging from ≥14 to ≥100 Hz, and reflecting normal consciousness characterised by alertness and cognition. Delta (>0 to <4 Hz) and theta (≥4 to <8 Hz) are associated with non-rapid eye movement (NREM) and rapid eye movement sleep. Relaxation and meditation are the hallmarks of the alpha band, which ranges from ≥8 to <13 Hz, so that any brainwave entrainment resulting in binaural beats of 10 Hz may be expected to encourage a relaxed (alpha) state of consciousness.

The rationale for our use of audiovisual stimulation, which added flickering light to the binaural beats, was that a

synchronous visual stimulus may reasonably be assumed to boost the auditory effect of brainwave entrainment. It has been shown that, in healthy volunteers who had their eyes closed, audiovisual stimulation (including binaural beats at 18.5 Hz) increased the power in the 13–21 Hz frequency band of the encephalogram by 49%, whereas auditory stimuli alone increased the power by only 21% as compared with the same measurements conducted without stimulation.[32]

Our approach in the present study was to match the frequencies we applied for brain stimulation to the electroencephalographic frequencies seen during NREM sleep. We selected 10 Hz as a departure point, which may be considered a fair approximation to the brain frequencies at this point, as the patients were asleep by the time of initiating the administration of propofol. Then, we reduced the frequency step-by-step, allowing the brain to synchronise with each new wavelength before applying the next decrement. Finally, at the bottom end of applicable frequencies, a steady state oscillating between 1 and 2 Hz was maintained to keep the brain continuously stimulated, assuming that any prolonged exposure to a totally unchanging frequency would be counterproductive.

BIS values, used to guide the dose reductions in the present study, are demonstrably useful in monitoring the depth of sedation achieved with propofol in paediatric surgery.[33] In fact, BIS monitoring of propofol anaesthesia has proved similarly reliable in children 1 yr or older as in adults.[34] Controversy still exists over its accuracy, given that the nervous systems of children are different from those of adults by the very fact that they are undergoing rapid development, as also reflected by typically more variable electroencephalograms. Previous research has disclosed two age groups for BIS monitoring under propofol anaesthesia, with 5–12 yr olds exhibiting lower values than up to 5 yr olds evaluated at the same time points.[35] With regard to our study, this means that any effect of age on these scores should have been minimal, considering that the eligible age range of 1–6 yr eventuated in only four children (two in either group) who were older than 5 yr.

Whilst the long-term implications of the present study are potentially revolutionary, its nature is clearly associated with medium-term limitations. Despite our point that many sedatives are not labelled for all age groups and may cause neuronal apoptosis, it should be understood that these risks mainly apply to very small children, whom we have been unable to study for the time being. Note that appropriate equipment is currently not available for children younger than 1 yr, let alone for neonates, and neither can BIS monitoring be suitably used with babies this young.

These limitations cannot, however, change the fact that the present study offers the first evidence of brainwave entrainment being capable *in principle* of generating effective results during paediatric surgery. We chose to investigate propofol,

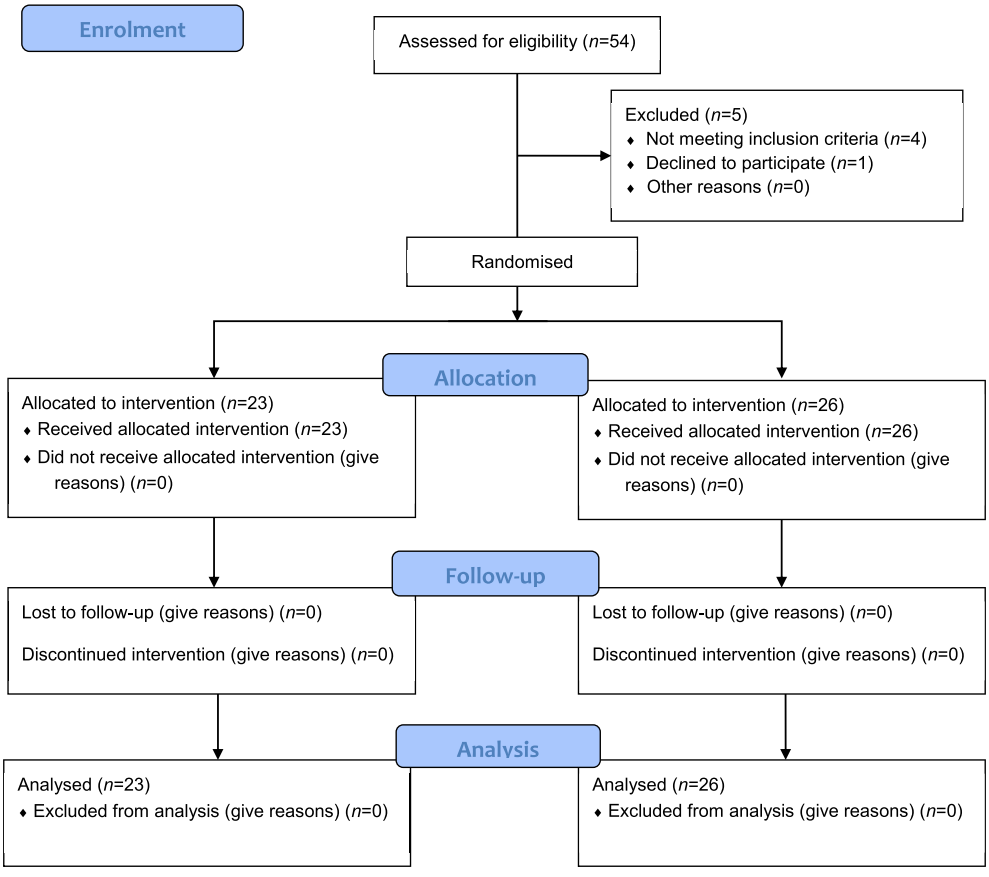

Fig 2. Consolidated Standards of Reporting Trials flow diagram.

which is widely used for procedural sedation and general anaesthesia in children. The use of a combination of drugs for sedation (e.g. sevoflurane, opioids, and α-2-receptor agonists), would have complicated the analysis and demonstration of effectiveness here provided.

Further studies are needed to investigate the possibility of further lowering sedative requirements. When surgery can be performed under local or regional analgesia, the ultimate objective would be to achieve sedation without the need for pharmacological interventions. Further investigations are needed to investigate the efficacy of entrainment, with propofol and other drugs, not only during longer surgical procedures, but also during other settings where sedation is used, such as the ICU or during brachytherapy. Finally, further studies are needed to determine the optimal choice of frequencies for brainwave entrainment.

Authors' contributions

Study design/analysis: PM, WK
Communication/administrative tasks related to ethics committee approval, the Austrian Agency for Health and Food Safety, and trial registration: WK
Clinical patient management: WS, WK, PO, MZ, LT
Data analysis/interpretation: WS, PM, WK, OK
Drafting of paper: WS, PM, WK

Declarations of interest

The authors declare that they have no conflicts of interest.

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