Does Caudal Bupivacaine Anesthesia Affect
The Depth of Pediatric Sevoflurane Anesthesia

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Abstract
Peripheral deafferentation induced by epidural or spinal anesthesia reduces the degree of cortical arousal in adults. This study aimed at determining if caudal blockade decreases the level of arousal, as measured by Bispectral Index (BIS) in unstimulated children and to determine if this effect differed between age groups. Hospital ethics committee approval and parental consent was obtained. Children (age range: 2-5 years) and infants (age range: 6-24 months) scheduled for below umbilical surgery that would usually require caudal local anesthesia block were recruited in the study. Before the procedure, subjects within each age group were randomized to either caudal group (1 mL/kg 0.25% bupivacaine), or control group (no caudal). In all groups, anesthesia was induced with sevoflurane and maintained at a constant end-tidal concentration of 1.5% sevoflurane without N2O. Five minutes after induction, a baseline BIS was recorded (BIS1). In the caudal groups, a caudal block was then performed while in the control groups no block was performed. Fifteen minutes later, the BIS was again recorded (BIS2). The change in BIS over this time period was the primary outcome (BIS3). After measurement, subjects in the control groups received a caudal block before the start of surgery. Twenty-nine infants and 18 children completed the study protocol. In children, BIS3 was significantly different between the caudal group and control (−5.7 vs. −0.7, P=0.04). In infants, no significant difference was detected in BIS3 between caudal and control groups. Caudal blockade decreased the degree of arousal, as measured by BIS, in unstimulated children aged 2-5 years. No change in arousal was detected in infants.

Introduction
During anesthesia, levels of cortical activity are determined by both the cortical concentration of anesthetic agent and the degree of subcortical stimulus or arousal. Regional anesthesia affects the degree of subcortical arousal via two mechanisms. The most important mechanism is ablation of nociceptive afferent traffic decreasing the arousal with surgical stimuli. A second, more subtle effect is via peripheral deafferentation, where arousal is reduced even in the absence of any surgical stimulus. In adults, several studies have investigated the effects of regional anesthetic techniques on arousal (in the setting of no surgical stimulus). Thoracic epidural blockade has been shown to reduce the minimum alveolar concentration (MAC) of sevoflurane, and also reduce the dose of sevoflurane required to achieve a Bispectral Index (BIS) score <50. Similarly, the degree of sedation observed in the presence of epidural blockade is dependent on the height of epidural blockade. Epidural bupivacaine has also been shown to decrease BIS in awake and anesthetized patients.

Caudal blockade is often combined with general anesthesia for pediatric surgery inferior to the umbilicus. Caudal blockade has also been described as a technique to provide sedation for infants during magnetic resonance imaging; however, no studies have objectively investigated the effects of caudal blockade on arousal. The aim of this study was to assess the effect of caudal blockade on arousal, as measured by BIS, in unstimulated children. The EEG changes with brain maturation and these age specific EEG changes may affect the ability of BIS to measure arousal. Therefore, the effect of caudal blockade on BIS was compared across two age groups.

Patients & Methods
This prospective study was conducted after approval from Human Research Ethics Committee at Abu Dhabi Health Authority Hospital and after obtaining written informed parental consent. The study comprised 54 children aged 6 months to 5 years and scheduled for
respect, the findings of this study may be consistent with previous findings that have demonstrated poorer relationships between BIS and measures of anesthesia effect in small children. \(^{6,7}\) Secondly, the number of subjects enrolled in this study was small. It is possible that there is a small effect in infants which the study had insufficient power to detect.

There are some limitations to this study. We allowed 15 min following administration of caudal blockade for bupivacaine to take effect. It is possible that any sedative effects of caudal analgesia may not be seen in this time. There are no published data describing onset time for caudal analgesia, however, clinical experience indicates the majority of caudal blocks are effective within this time. The time from BIS\(_1\) to BIS\(_2\) was longer in the caudal groups across all ages. This was because of an underestimation of how long it would take to perform the caudal block (interestingly they were slowest in infants). In general, BIS\(_2\) tended to be lower than BIS\(_1\) in all control groups indicating a tendency for the BIS to fall with time. This fall, however, was small and the extra 2–3 min was unlikely to have influenced the result.

Local anesthetics in the epidural space may effect arousal via three mechanisms. First, it may be because of deafferentation of peripheral input; secondly, it may be that direct effect of the local anesthetic on the brain after rostral spread of local anesthetic in the CSF and thirdly, as the effect of the local anesthetic delivered to the brain after systemic absorption into the circulation. Animal studies have demonstrated that there is little CSF spread. \(^{8}\) Administration of local anesthetic intravenously or intramuscularly has been shown to have sedative effects. \(^{9-12}\) It is unclear how much the sedative effect of epidural local anesthetic is caused by systemic absorption. In Hodgson's study, the MAC-sparing effect of epidural lignocaine was found to be greater than the equivalent dose given intravenously. \(^{13}\) It is possible that in children higher peak plasma concentrations are found compared with adults and that systemic effect may be greater. If this were true then the lack of effect seen in infants in our study may be because of differences between children and infants in the absorption or clearance of the local anesthetic.

In this study, the BIS at 1.5% sevoflurane was different between age groups. In the study design, we did not adjust the concentration for age as constant MAC values have been described for sevoflurane over these age groups. \(^{13}\) Interestingly, this age-related discrepancy between MAC and EEG has since been described elsewhere. \(^{6,14,15}\) The age-related discrepancy between MAC and EEG is of considerable interest and relevance when discussing changes in anesthesia effect with brain maturation. When using the BIS as a measure of arousal, it must be emphasized that BIS is an empiric derivative. It is therefore best regarded, whenever possible, as an ordinal, not interval scale. The difference between a BIS of 70 and 60 is not the same as a difference between 60 and 50. In our study the baseline BIS (BIS\(_1\)) differed between infants and children. Given this difference in baselines, and the ordinal nature of BIS, it is unclear if differences in magnitude from different baselines are directly comparable. In infants, there was also a marked reduction in the spread of BIS values in the caudal group compared with the control group. The reason for this is unclear.

Wherever possible in this study, nonparametric tests were used to compare BIS values. This is the preferable, and the most conservatve way to treat BIS values. However, 2-way ANOVA was used for the original analysis, as there is no recognized non-parametric alternative. Similarly, to test for the effect of selected non-controlled demographic variables a multivariate regression analysis was used. A linear regression analysis makes substantial assumptions about the nature and distribution of the data, therefore compared with the primary outcome analysis, the results of this multivariate linear regression are much less certain. When interpreting this study (and any other study), which uses BIS, the assumptions in the statistical analysis
made about the nature of BIS must be considered, particularly when the evidence for a result is borderline. In this study, we took a conservative approach.

The implications from this study are that caudal blockade is likely to increase levels of sedation in children between 2 and 5 years; therefore anesthetic concentrations required to produce unconsciousness are less when there is an effective caudal block. Physiological studies in children are difficult for ethical reasons. When studying the pharmacodynamics of anesthetics in children, anesthesia with neuraxial blockade may have been an attractive model for unstimulated anesthesia. The result of this study, however, indicates that when using this model, the effect of deafferentation needs to be considered.

In conclusion, 1 ml/kg of 0.25% bupivacaine induced a decreased level of arousal, measured by BIS, in children aged 2–5 years. A similar decline in the level of arousal was not observed in infants.

References
11. Tverskoy M, Ben-Shilomo I & Vainshtein M (1997): Hypnotic effect of i.v. thiopentone is enhanced by i.m. administration of either lignocaine or bupivacaine. Br J Anaesth; 79: 798–800.
with the exceptions of sex and use of midazolam (for which Fisher's exact test was used) and comparing BIS (where the Wilcoxon rank-sum test was used). Where differences in potentially confounding demographical variables were found between groups, these variables (along with age and study group) were entered into a separate multivariate linear regression analysis to reassess the association between caudal, age and BIS when adjusted for the potentially confounding demographical variables.

Results

Of the 54 patients recruited, seven were excluded from analysis because of protocol violations or technical failures, leaving 29 infants and 18 children. The seven patients excluded from analysis included four violations of the anesthesia protocol, such as use of nitrous oxide or propofol, one patient who violated exclusion criteria (suspected neurological abnormality), and one instance of equipment failure. The study was also abandoned in one case following excessive movement in response to placement of the caudal needle. There were no significant differences between control and caudal groups in age, sex, use of premedication, end tidal CO₂ and temperature (Table 1).

No significant differences were observed in BIS between control and caudal groups in either age group (Table 2). The time from induction of anesthesia to the first period of BIS measurement (Time₁ᵢₙ₋₁) was not significantly different between control and caudal groups, in either age group. The time from BIS₁ to BIS₂ (Time₁₋₂) was 2.7 min longer in the caudal group in infants (95% CI: 1.2-4.1 min, \(P < 0.001\)) and 2.3 min longer in the caudal group in children (95% CI: 0.003-4.6 min, \(P = 0.05\)).

The two-way ANOVA comparing BIS between study and age groups indicated there was no significant difference detected between caudal and control groups adjusting for age (\(P = 0.6\)), and no significant difference detected between age groups adjusting for study group (\(P = 0.6\)). However, from the two-way ANOVA analysis, there was evidence of a differential effect of the caudal according to age group (there was a significant interaction between study group and age, \(P = 0.034\)).

When caudal and control groups were separately compared in each age group, there was some evidence for a greater fall in BIS (BIS₃) in children in the caudal group compared with children in the control group (\(-5.7 \text{ vs. } -0.7, P = 0.038\)). There was no evidence for any difference was between caudal and control groups in infants (\(P = 0.6\); Table 3 and Figure 1).

When caudal and control groups were combined, there was strong evidence \((P < 0.0001)\) that the median BIS scores in infants (70.1, 95% CI: 68.5-70.9) were higher than the median BIS scores in children (58.5, 95% CI: 53.5-63.1).

As there were differences across age and study groups in Time₁₋₂ and BIS₁, these two variables were included in the multivariate linear regression model along with age group, study group (caudal or control) and an interaction factor between study group and age group. In this regression, neither Time₁₋₂ nor BIS₁ had a significant association with BIS in infants \((P = 0.2\) and \(P = 0.2\) respectively), and adjusting for their inclusion did not decrease the evidence for the interaction between study group and age \((P = 0.03)\).

Discussion

Our results indicate that in children aged between 2 and 5 years of age, caudal blockade decreases the level of arousal as measured by BIS. This is consistent with previous adult studies demonstrating decreased BIS scores and reduced anesthesia requirement following neuraxial blockade. In children, the drop in the caudal group was approximately 5 BIS points greater than the drop in the control group. It is unclear if such a difference has clinical significance.

The lack of change seen in infants has a number of possible explanations. First, there are some data to suggest the performance of BIS differs in younger children. In young children, it is possible that caudal analgesia does affect arousal, but BIS does not detect the change. In this
respect, the findings of this study may be consistent with previous findings that have demonstrated poorer relationships between BIS and measures of anesthesia effect in small children.1,5,6 Secondly, the number of subjects enrolled in this study was small. It is possible that there is a small effect in infants which the study had insufficient power to detect.

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