Original Article

Hippocampal volume and recovery profile following propofol sedation in children undergoing magnetic resonance imaging: An exploratory study

ABSTRACT

Background: Reduction in the hippocampal volume may contribute to agitated and delayed emergence after anesthesia in epilepsy surgery. We hypothesized that hippocampal volume and the duration of various recovery parameters after a short duration of sedation may be correlated. The primary objective was to evaluate the correlation between hippocampal volumes with time to recovery after the stoppage of propofol infusion.

Methods: After obtaining Institute Ethical Clearance, we included all children of the age group 5–17 years, who needed sedation for brain magnetic resonance imaging (MRI) for at least 20–60 minutes for the evaluation of epilepsy. The hippocampal volume was estimated bilaterally in the pre-contrast volumetric magnetization-prepared rapid gradient-echo (MPRAGE) brain imaging by the radiologist using statistical parametric mapping. The correlation of hippocampal volume with recovery and time to discharge (assessed by the modified Aldrete score (MAS)) was obtained using Spearman's correlation coefficient (rho). A rho > ± 0.5 was considered a good correlation between the variables.

Results: Data on a total of 18 children (10 males and 8 females) who required sedation for an MRI were studied over a period of six months. The correlation coefficients of right and left corrected hippocampal volumes with time to spontaneous eye opening were -0.052 and -0.195, respectively. The correlation coefficients of right and left corrected hippocampal volumes with time to respond to oral commands were -0.017 and -0.219, respectively.

Conclusion: There was a weak negative correlation between hippocampal volumes and recovery parameters after a short duration of sedation with propofol in children.

Key words: Hippocampus, modified Aldrete score, propofol, recovery, sedation

Introduction

Arousal and maintenance of organized behavior during wakefulness are regulated by the central thalamus area of the ascending pathways from the brainstem and basal forebrain and descending pathways from the cortex.[1] The hippocampus and nucleus ambiguus play an albeit

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modest yet significant role in active waking behaviors and emergence from sedation and anesthesia.[2] Hippocampal volume might play a definitive role in emerging from anesthesia delayed awakening, amnesia, postoperative delirium, and postoperative cognitive decline.[3] In a study involving mice, electrical activity patterns involving the hippocampus and prefrontal cortex provide important clues about the involvement of these structures in arousal.[4] Hippocampal volume reduction in elderly patients is linked to the development of postoperative cognitive dysfunction.[3] Previously, an unpublished study showed that the reduced hippocampal volume may contribute to agitated emergence after anesthesia following epilepsy surgery.[5] The hippocampal electrical activity is shown to have a direct correlation with sleep, wakefulness, and arousal after anesthesia.[6] Several molecular and electrophysiological studies have shown that various factors (sevoflurane/etomidate anesthesia and temporal lobe resection leading to hippocampal atrophy in epilepsy patients) affect hippocampal cells or electrical activity and may cause a delay in recovery from general anesthesia.[4] Delayed recovery/emergence from anesthesia is the abnormally slow pace of regaining consciousness after general anesthesia, which is characterized by persistent somnolence.[7] Delayed recovery is a challenge that anesthesiologists are confronted with, as it requires additional time to analyze and use of additional resources to identify the cause. The delay in recovery of the patients from sedation leads to an increased duration of stay in the post-procedure room, increased need for additional monitoring and care, and increased duration of hospital stay.

Very often delayed recovery after hippocampal resection surgery is encountered in patients, which prompted our research team to investigate the relationship between volume of hippocampus and delayed recovery after surgery. Hence, the team wanted to establish the effect of hippocampal volume and recovery characteristics after a short course of sedation. The hippocampal volume can be estimated using magnetic resonance imaging (MRI), which can be correlated with the recovery process after sedation with anesthetics, such as propofol. In this exploratory study, we hypothesized that the hippocampal volume and the duration of recovery based on various parameters may be correlated directly or inversely. The primary objective was to evaluate the correlation between hippocampal volumes with time to recovery after the stoppage of propofol infusion. The secondary objective was to evaluate the relationship between hippocampal volume with the time to discharge after propofol sedation from the post-procedure room and the effect of hippocampal volume with delayed recovery.

Methods

Our manuscript adheres to the STROBE guidelines. After obtaining approval from the institutional ethics committee, we enrolled the patients. This study was registered in the Clinical Trials Registry of India (CTRI) [CTRI/2021/07/034647]. We conducted this prospective observational cohort study with the following inclusion and exclusion criteria.

The inclusion criteria are as follows:

- All pediatric patients of age group 5–17 years, who needed sedation to undergo brain MRI for the evaluation of epilepsy
- Patients receiving sedation for 20 to 60 minutes of duration.

The exclusion criteria are as follows:

- Refusal to obtain informed consent
- Patients with modifiable causes of delayed recovery, such as hypothyroidism, hyponatremia (serum sodium concentration [Na^+] <135 mEq/L), hypernatremia ([Na^+] >145 mEq/L), hypo/hyperglycemia, and hypothermia with axillary temperature of $<35°C$
- Patients with known liver and/or renal dysfunction (defined as elevated or aspartate aminotransferase/alanine aminotransferase >5 times[8] serum creatinine >1.2 mg/dL)[9]
- Patients on inotropic support
- Patients who were intubated
- Patients with the motor component of Glasgow coma scale (GCS) score ≤ 5 and the eye component <4
- Patients diagnosed with intracranial space-occupying lesions
- Patients following intracranial surgery/or resection surgery.

All eligible children were thoroughly evaluated before the procedure, and a preanesthetic checkup was performed. Informed consents were obtained from their legal guardian. There were no interventions as this was an observational study, and periprocedural care of these patients was carried out as per the standard institute practice. According to the Standard American Society of Anesthesiologists, noninvasive blood pressure, electrocardiogram (ECG), pulse oximetry (SpO_2), and end-tidal carbon dioxide were monitored. All patients were sedated with a bolus dose of propofol (Neorof®, Neon Laboratories Limited, Mumbai, India) at 1–1.5 mg/Kg of body weight followed by a maintenance infusion dose of propofol titrated to maintain an Observer's Assessment of Alertness/Sedation (OAA/S) Scale score of 2 using an MRI compatible syringe pump (B. Braun SpaceStation MRI®, Melsungen, Germany), following which an MRI was performed. In case

of any movements while performing the scan, bolus doses of propofol at 0.5 mg/kg were supplemented and the number of movements and number of dose adjustments were recorded. After the completion of the MRI scan, the infusion was stopped and the time was noted. The patients were shifted to the post-procedure room for observation and monitoring.

Brain imaging was performed on a 3 Tesla MRI scanner (Siemens Magnetom VIDA 3.0T, Siemens Healthineers, Erlangen, Germany). The hippocampal volume was calculated bilaterally in the pre-contrast volumetric magnetization-prepared rapid gradient-echo (MPRAGE) sequence of brain imaging by the radiologist using statistical parametric mapping. Images were acquired on 192 sections, with a field of view (FOV) of 230 × 230 and 0.9 mm slice thickness in sagittal orientation. The time for acquisition of the sequence is estimated to be 6 minutes 11 seconds (repetition time {TR} = 3000 ms, time to echo {TE} = 3.41 ms, voxel dimension = 0.9 × 0.9 × 0.9 mm). We corrected the hippocampal volumes with respect to total intracranial volume (ICV) helping to define subtle differences in total hippocampal volumes and to compensate for growth-related hippocampal volume changes. We followed the methodology and formula provided by Jalaluddin WM *et al*.[10] to correct the hippocampal volumes.

The data were collected from the beginning of sedation to turning off the infusion and until discharge from the post-procedure room. The patients were discharged only after the target OAA/S of 5 and the modified Aldrete score (MAS) of ≥9 were achieved. We collected data on heart rate, blood pressure, SpO_2, and OAA/S 5 minutes after the stoppage of the infusion and every 2 minutes up to a point where the patient became fit for discharge from the procedure room. The total propofol dose used until the stoppage of infusion was recorded.

The assessment of recovery was performed without any stimulation (tactile or noxious). The time to spontaneous eye opening and response to oral commands by the patients were recorded from the time of stoppage of infusion. We defined delayed recovery as being unable to spontaneously open eyes 10 minutes after the stoppage of infusion.

The assessment of adequacy to discharge was made as per the MAS, which tests the activity level at request.

All statistical analyses were performed using SPSS software (version 20). The correlation of hippocampal volume with recovery and time to discharge (obtained by time to recovery characteristics and MAS) was obtained using Spearman's correlation coefficient. The association of hippocampal volume with time to recovery was assessed using the Mann–Whitney U-test. We analyzed the data utilizing both the uncorrected and corrected hippocampal volumes (corrected for ICV).[10] A rho > ± 0.5 was considered a good correlation between the variables. A P value < 0.05 was considered significant.

Results

In the study period, we collected data on a total of 18 children (10 males and 8 females), who required sedation for an MRI. The median duration of sedation was 42.5 min in these children. In terms of the recovery characteristics, the median duration for time to eye opening was 15 min, while the median time taken to respond to the oral commands was 16.5 min. The children post-sedation required a median of 16 min to achieve a MAS ≥9 [Table 1].

The correlation coefficients (rho) of right and left corrected hippocampal volumes with time to spontaneous eye opening were -0.052 and -0.195, respectively. The correlation coefficients of right and left corrected hippocampal volumes with time to respond to oral commands were -0.017 and -0.219, respectively [Table 2].

We calculated the correlation coefficients of corrected hippocampal volumes with respect to time to discharge from the recovery room (MAS ≥9) after propofol sedation. The correlation coefficients of corrected right and left hippocampal volumes with the time to achieve MAS ≥9 were -0.102 and -0.138, respectively [Table 2].

Interestingly, we noticed that children who had a delayed recovery had a lesser hippocampal volume as compared to children with normal recovery, although statistically not significant. The sedation duration was comparable between the two groups. However, the total dose of propofol was higher in the group that had normal recovery [Table 3].

Table 1: Demographics and clinical characteristics of the patients (data are presented as median (interquartile range))

	Total (n=18)
Age (years)	7 (6-11)
Gender (male)	10 (55.5%)
Weight (Kg)	21 (15-29.5)
ASA	2 (1-2)
Duration of sedation (minutes)	42.5 (34-54.25)
Recovery characteristics	
Time to eye opening (min)	15 (4.25-21.75)
Time to respond to oral commands (min)	16.5 (5-25.5)
Time to achieve MAS ≥9 (min)	16 (6.5-24.5)

ASA=American Society of Anesthesiologists, MAS=Modified Aldrete score

Table 2: Spearman's correlation of coefficient (rho) of hippocampal volumes with the recovery parameters of the patients

	Time to spontaneous eye opening	Time to respond to oral commands	Time to discharge (MAS ≥9)
Right hippocampal volume	-0.133	-0.114	-0.141
Left hippocampal volume	-0.203	-0.227	-0.144
Corrected right hippocampal volume	-0.052	-0.017	-0.102
Corrected left hippocampal volume	-0.195	-0.219	-0.138

Table 3: Association of different variables with recovery (data are presented as median (interquartile range))

	Normal recovery (n=8)	Delayed recovery (n=10)	P
Age (years)	9.5 (6.25-14.75)	7 (6-10.25)	0.408
Gender (male)	2 (25%)	8 (80%)	0.394
Weight (Kg)	22.5 (15-40.75)	21 (17.25-25)	0.762
Duration of sedation	41 (37-54.25)	42.5 (30.75-54.5)	0.829
Total propofol dose (mg)	207.5 (94.9-334.38)	121.5 (93.48-188.25)	0.274
Time to eye opening (minutes)	3.5 (2-7.75)	19.5 (16.5-28.5)	0.001
Time to respond to oral command (minutes)	5 (2.25-9.75)	23 (17.75-29.75)	0.001
Time to achieve MAS* ≥9 (min)	6 (5-10.5)	21 (16.5-29.5)	0.009
Right hippocampal volume (mm^3)	3367 (2284-3724.5)	2875.5 (2481-3703.5)	0.460
Left hippocampal volume (mm^3)	3289 (2715.25-3610.5)	2884.5 (2650.75-3378)	0.573
Corrected right hippocampal volume (mm^3)	3426 (2953-3751.75)	3041 (2599-3808.75)	0.663
Corrected left hippocampal volume (mm^3)	3289 (2744.5-3607)	2928.5 (2682.25-3390.75)	0.573

*MAS=Modified Aldrete score. $P<0.05$ is considered significant

Discussion

The process of recovery from anesthetics or sedative agents depends on several factors. In this study, we tried to identify one of the several anatomical factors, that is, estimation of hippocampal volume, which is related to the process of emergence and arousal. The hippocampal volume estimation in this study was performed to identify the existing correlation with recovery characteristics. The study was conducted in children who required an MRI for the evaluation of epilepsy, where we could easily perform the volumetric analysis of the hippocampus. We corrected the volume of hippocampus with respect to the ICV using the normalization formula[10] so that the growth-related bias in volume estimation was nullified. In this study, we chose the time to spontaneous eye opening and response to oral commands as a gauge for recovery from sedation. The MAS ≥9 was used for discharge criteria from the MRI holding area.

We evaluated the correlation of the hippocampal volume with time to spontaneous eye opening, which showed a weak negative correlation with the left hippocampal volume. Similarly, the time to oral response and MAS ≥9 showed a weak correlation with the left hippocampal volume.

However, when the association of hippocampal volume was tested with the delayed versus normal recovery group, we found that a reduced volume of hippocampus was associated with delayed recovery, which, however, did not attain statistical significance.

In a previously unpublished conference abstract, the authors found that the reduced hippocampal volume was associated with agitated emergence from anesthesia after epilepsy surgery.[5] They did not find the correlation coefficient in their study. The difference in this study is that we have tried to correlate hippocampal volume after a short duration of sedation unlike after a complete duration of surgery. Patients underlying neurologic status and drug levels can all contribute to delayed recovery and emergence agitation. In our study, there was no difference in the total dose of propofol used among the delayed and normal recovery groups in the pediatric cohort [Table 3]. We also noticed that the normal recovery group had received more propofol as compared to the delayed recovery group, which points toward their underlying anatomical or structural differences, such as smaller hippocampal volumes. In another study involving elderly individuals, who were followed and evaluated till 4th postoperative day, the authors concluded that reduced hippocampal volume before surgery was associated with the development of POCD.[3]

Strengths and limitations

The study's unique strength is that it is the first kind of study where this correlation was performed to relate hippocampal volume with recovery after a short duration of sedation with propofol. However, the small size of the cohort can be a limitation of this analysis.

Conclusion

We conclude that there is a weak correlation between hippocampal volumes and recovery parameters after a short duration of sedation with propofol in patients undergoing MRI. This observation can serve as a guide for future studies to evaluate the association between the hippocampus and process of recovery after sedation.

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Conflicts of interest
There are no conflicts of interest.

References

1. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med 2010;363:2638-50.
2. Leung LS, Luo T, Ma J, Herrick I. Brain areas that influence general anesthesia. Prog Neurobiol 2014;122:24-44.
3. Chen M, Liao Y, Rong P, Hu R, Lin GX, Ouyang W. Hippocampal volume reduction in elderly patients at risk for postoperative cognitive dysfunction. J Anesth 2013;27:487-92.
4. Butovas S, Rudolph U, Jurd R, Schwarz C, Antkowiak B. Activity patterns in the prefrontal cortex and hippocampus during and after awakening from etomidate anesthesia. Anesthesiology 2010;113:48-57.
5. Banik S, Bharadwaj S, Manninen P, Valinate T, Venkatraghavan L. Hippocampal volume determines the quality of emergence from anesthesia. Available from: http://www.casconference.ca/en/wp-content/uploads/sites/2/2018/06/ Neuro-452293.pdf. [Last accessed on 2022 Oct 17].
6. Green JD, Arduini AA. Hippocampal electrical activity in arousal. J Neurophysiol 1954;17:533-57.
7. Misal US, Joshi SA, Shaikh MM. Delayed recovery from anesthesia: A postgraduate educational review. Anesth Essays Res 2016;10:164-72.
8. Koyama T, Hamada H, Nishida M, Naess PA. Defining the optimal cut-off values for liver enzymes in diagnosing blunt liver injury. BMC Res Notes 2016;9:41.
9. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol 2002;13:2140-4.
10. Jalaluddin WMS, Mat Jusoh N, Ali Basahai IA, Abdullah MS, Karim AHA, Gazali AK. Normalised MRI volumetry of the hippocampus among normal malay children and adolescents. Malays J Med Sci 2013;20:31-8.