Postoperative cognitive recovery in children after both general and locoregional anesthesia and surgery

Jalal El Hammoumi

FMPF

Abdelkader Dahchour

FMPF

Elmehdi Chhiti

FMPF

Saïd Benlamkadem

FMPF

Mohamed-Adnane Berdai

FMPF

Mustapha Harandou

FMPF

Saïd Boujraf (✉ sboujraf@gmail.com)

University of Sidi Mohamed Ben Abdellah

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Abstract

Background and objectives

Recent researches have demonstrated that there is a progressive impairment in neurocognitive function following general anesthesia and surgery, and particularly, have evidenced that anesthetics impaired mechanisms of learning and memory, for days to months, in both adults and children.

This study aimed to evaluate the influence of different types of anesthesia (General or Locoregional) on cognitive recovery by trial and error method, and also take into consideration other factors that would have an impact on the cognitive performance after anesthesia and surgery in children.

Methods

In the present cross-sectional study, 64 young children, aged between 10 and 15 years, have passed the CALM test (software based on trial and error method) 24h after their surgery, and the operating file filled by the anesthetist. The statistical analysis includes a descriptive part of our sample, a univariate, and multivariate analysis of the results of the CALM test and the various medical factors and lifestyles.

Results and conclusions

The cognitive performance of patients exposed to locoregional anesthesia (81.3%) was higher ($p=0.01$) when compared to patients under general anesthesia (34.4%). Both agitation (Neurological state) and postoperative pain significantly ($p=0.02$) altered the cognitive performance of patients. However, none of the other factors assessed such as gender, environmental living, schooling, pre-anesthetic consultation, and the type of intervention affects the postoperative cognitive performance of patients.

Locoregional anesthesia has less effect on cognitive recovery when compared to general anesthesia. Both the postoperative pain and agitation alter cognitive performances of operated children.

Background

Researches using different animal models reported that general anesthetics and sedatives cause neuronal damage to the developing brain, even neuronal death and can cause long-lasting impairment of learning and memory when exposed in the early postnatal period (Fredriksson et al. 2007; Zou et al. 2009; Zhu et al. 2010; Paule et al. 2011; Yu et al. 2013; O'Farrell et al. 2018).

Several suggested molecular and cellular mechanisms explaining how anesthetics-induced neurotoxicity occurs? And how does these affect behavioral and cognitive abnormalities? Among these mechanisms:

Acceleration of anesthesia-induced apoptosis by activating GABAA receptors, in the period when it is excitatory (Edwards et al. 2010; Xie et al. 2017), and by blockade of the NMDA receptor, during the corresponding period (Ikonomidou et al. 1999; Rudin et al. 2005; Takadera et al. 2006; Wang et al. 2006).

Anesthetics have been shown to enhance reactive oxygen species (ROS) production (Bai et al. 2012; Boscolo et al. 2013), impair mitochondrial structure and function (Zhang et al. 2010; Sanchez et al. 2011; Bai et al. 2013), and to induce neuroinflammation particularly when followed by surgery (Wan et al. 2007; Shen et al., 2013; Boscolo et al. 2013), decrease in brain-derived neurotrophic factor (Brambrink et al., 2012; Dalla Massara et al. 2016; Wu et al. 2016; Liu et al. 2018)

Recent studies showed that microRNAs are responsible, in part, in anesthetic-induced developmental neurotoxicity (Cao et al. 2015; Xu et al. 2015; Jiang et al. 2014; Huang et al. 2014; Twaroski et al. 2014; reviewed by Kreth et al. 2018; Zhao et al. 2018).

All these events or one of them can trigger neuronal destructive process. It is well established that general anesthetics impede neurogenesis, synaptogenesis, axonal growth (Sall et al. 2009; Zhu et al. 2010), and damage glial cells, such as oligodendrocytes and astrocytes (Brambrink et al., 2012; Culley et al., 2013; Ryu et al., 2014). Subsequently, promote long-lasting behavioral and cognitive disabilities that persist into adolescence and adulthood (Jevtovic-Todorovic et al. 2003; Lin et al. 2016; Xiao et al. 2016; Zhao et al. 2018; Zhou et al. 2019).

Although there is far from a consensus made on the association between exposure of young children to anesthesia and the long-term consequent impairment in neurocognitive functions; there are increasing concerns with the use of anesthetic agents particularly in developing period, and some of these studies have evidenced this association (Wilder et al. 2009; DiMaggio et al. 2011; Sprung et al. 2012; Backeljauw et al. 2015; Zhang et al. 2017; Schneuer et al. 2018), and others did not (Bartels et al. 2009; Sun et al. 2016).

Accordingly, and referring to a review of both preclinical and clinical studies, the US Food and Drug Administration (FDA) has issued a safety warning that exposure to anesthetics and sedatives in children, before 3 years of age, may have long-lasting damaging effects on cognitive functions (FDA, 2016). Consequently, additional studies are needed to identify if the observed association is due to the anesthetics themselves or other factors or conditions around both anesthesia and surgery? And if there are alternatives to general anesthesia (GA) when professionals have the choice?

To address these questions, the present study compares the effect of GA versus locoregional anesthesia (LRA) on the recovery of cognitive impairment by the test-error method in children considering the factors that would have an impact on cognitive performance in postoperative period, of children who had experienced anesthesia and surgery compared to those who had not.

Methods

This is a cross-sectional study that looked at patients who underwent either GA or a LRA. The study conducted between January and May 2018 at the hospital Hassan II-Fes, pediatric surgery block. The selection of patients respected the minimum number representative for each type of anesthesia. The phase of the data collection was as follows: Anesthesiologist should fill trial registry which contains

essential information of the patient, and then, 24 hours after the surgery, which lasts 1 h in all cases, patients pass the CALM test. Our goal was to evaluate the cognitive recovery of anaesthetized patients and the problems caused by anesthesia on their learning.

Anesthetic agents

For GA the following agents were used: Fentanyl 50 mg /cc; Propofol 20 mg/cc; Esmeron 50 mg/5 cc (Rocuronium bromide).

For LRA anesthesia the following agents were used: Bupivacaine, (Marcaine) 0.25% and Lidocaine (Lignocaine) 2%

Statistical analysis

Statistical analyses were performed with SPSS software at Laboratory of Clinical Neuroscience, in the Faculty of Medicine and of Pharmacy of Fez, Morocco.

A univariate analysis was carried out to study the association between the patient performance (binary dependent variable) and the various variables collected through this study. The statistical significance of these associations was judged by the test ANOVA at the 5% threshold. Associations, raw and adjusted between variables categorical and patient performance were analyzed by a logistic regression.

Visual analogue scale (VAS)

The postoperative pain (POP) was evaluated by Visual Analogue Scale (VAS) which is a numerical rating scales from 0 to 10 cm was used to measure pain intensity (Li et al. 2007). Patients with a VAS score of less than 3 ($VAS < 3$), have a mild pain, while patients with VAS greater than or equal to 3 ($VAS \geq 3$) are considered to have a severe pain.

Ethics approval

Written consent was obtained for each patient from the parent or legal guardian of the children, while verbal consent was obtained from the teenager participant together with an explanation that was provided in written and verbal forms of consent to participate. Indeed the study was conducted according to the guidelines and recommendation of the local ethical committee. The local ethical committee and national regulation regarding the ethical approval are complying with the international standards including the National institute of Health (USA) standards.

in the “Method “and “Ethics approval and consent to participate” section of the Declarations.

Results

The postoperative pain (POP) as evaluated by Visual Analogue Scale (VAS) score was significantly different ($p = 0.02$) when comparing general and locoregional anesthesia effect. 84.4% of patient under

LRA reported a mild pain (VAS < 3) and only 15.6% reported a severe pain (VAS ≥ 3). However, 65.6% of patient under GA reported a severe pain (VAS ≥ 3) and 34.4% reported a mild pain (VAS < 3).

The type of anesthesia (GA / LRA) significantly affects the NS of patients ($p = 0.02$). 75.0% of patients under GA were agitated at the wake up by comparison to patients under LRA (21.9%).

The type of anesthesia did not imply any influence on all of the other factors evaluated such as: Age; Sex; Life environment; Schooling; Pre-anesthetic consultation the patient, and the type of intervention.

Results of the descriptive statistical analysis of CALM test

The totality of the patient did not encounter any traumatic accidents of anesthesia in the operating room (shock hemorrhagic, heart problems ...), which increases the credibility of the degrees of performance of our patients.

The CALM software test evaluated the learning of the patients using the trial and error model and revealed variable patient performance depending on the type of anesthesia.

In this study, the patient is considered to be performing if (test time / mean time per test) does not exceed 50 minutes.

The type of anesthesia (GA / LRA) significantly affects the cognitive performance of patients ($p = 0.01$). Patient exposed to LRA had better cognitive performance (81.3%) than patients exposed to GA (only 34.4%).

The POP, as evaluated by Visual Analogue Scale (VAS), significantly affects the cognitive performance of patients ($p = 0.02$). Patients with severe pain (VAS ≥ 3) display less performance (42.3%) when compared to patient reporting a mild pain (VAS < 3) (68.4%).

The NS of patients significantly affects the cognitive performance of patients ($p = 0.02$); in fact, calm patients showed better cognitive performance (66.7%) than anxious and agitated patient (48.4%).

The type of anesthesia (GA / LRA) significantly affects ($p = 0.02$). The type of anesthesia did not imply any influence on all of the other factors such as: Age; Sex; Life environment; Schooling; Pre-anesthetic consultation the patient, and the type of intervention.

The results of the univariate analysis were followed by a multivariate analysis to ensure their reliability. Associations between different factors and the performance of anesthetized patients were analyzed by logistic regression.

OR: Odds ratio; CI: Confidence Interval; VAS: Visual Analogue Scale (for pain)

Patient's performance is associated with their POP (VAS score) [OR = 13.176; $p = 0.01$], their neurological status (Calm/agitation) [OR = 0.74; $p = 0.02$], and with the type of anesthesia (General or locoregional)

[OR = 0.12; p = 0.01].

Discussion

In this study, we evaluate the influence of the type of anesthesia (GA and LRA) on cognitive recovery from surgery, in children aged from 10 to 15 years old, using a trial and error method.

The results showed that children who were exposed to LRA showed better postoperative analgesia (84.4%) and better cognitive performance (81.3%) than others undergone GA who have worse postoperative analgesia (34.4%) and worse cognitive performance (34.4%).

This study also showed that the NS of children exposed to anesthesia and surgery was differentially affected by the type of anesthesia (78.1%) of patients were calm with LRA and only 25% in GA and 75% of patients were agitated with GA and only 21.9% with LRA and by consequence influenced the cognitive performance of patients. Calm children were better cognitive performing (66.7%) than agitated patients (48.4%).

Data from our study are consistent with those of clinical studies showing that pain, associated with surgery, could contribute to the development of postoperative cognitive dysfunction (POCD). For example, in a population aged 65 years or older (Wang et al. 2007) and could impair neurocognitive performance in chronic pain simples (reviewed by Higgins et al. 2018). Furthermore, Zywił et al., in a systematic review, concluded that both anesthetic and pain management strategies do appear to affect the risk of POCD in patients enduring elective joint arthroplasty (Zywił et al. 2014). In opposition, Aun et al. found that the prevalence that GA elicits POCD on the first day and at 6 weeks after non-cardiac surgery in children aged 5 to 12 years, was low (Aun et al. 2016). Zhang et al. concluded that more than 3 hours' exposure to GA (not short- and moderate-duration) influenced the IQ of children aged 6–12 years, for up to 3 months after orthopedic surgery (Zhang et al. 2017). As we can notice from this study, even if it is in concordance with our data, the time of exposure to GA in this study is triple than in our study.

Our results are not consistent with other clinical studies considering the exposure of children to GA at their early age, and the long term outcome. For example, Glatz et al. in a study cohort of 33 514 children showed that exposure to a single anesthesia and surgery before age 4 years has a small association with their later (at age 16 years) academic performance or cognitive performance (IQ test scores) (Glatz et al. 2017). As well as in the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study, in which children exposed to a single GA at the age of 3 years, did not alter IQ scores in later childhood at 8 to 15 years old (Sun et al. 2016). The results of both primary (McCann et al. 2019) and the secondary (Davidson et al. 2016) outcome of the General Anesthesia compared to Spinal anesthesia (GAS) study, also, concluded that the exposure of children for 1 hour to GA in their early infancy does alter neurodevelopmental outcome neither at 2 nor 5 years old later when compared with awake-regional anesthesia. One of the major differences between these studies and ours is that these studies aimed the long term outcomes, in contrast to our study in which the measurement of the effects was short term 24 hour after anesthesia and surgery. However, repeated exposure to anesthesia, at younger age, could

increase the risk to developing postoperative disabilities (Flick et al. 2011). As Wilder et al. study showed, children who had more than one, exposure to anesthesia and surgery before age 4 years were at double risk, at their late age 19 years, to develop learning disabilities when compared with children not exposed to anesthesia (Wilder et al. 2009).

Our study showed that the POP significantly influenced the cognitive performance of children exposed to anesthesia and surgery, since patients expressed a mild POP were better cognitive performing (68.4%) than patients that exhibited severe pain (42.3%). This is in agreement with preclinical and clinical studies confirming that pain experience is associated with cognitive impairment (Reviewed by Moriarty et al. 2011). Furthermore, according to animal studies, surgical incision-induced POP triggered learning impairment and memory function (Zhang et al. 2013; Liu et al. 2018; Xu et al. 2014). This is due probably by activating oxidative stress and mitochondrial dysfunction (Netto et al. 2018), inhibiting the brain-derived neurotrophic factor (BDNF) signaling pathway (Saffarpour et al. 2017; Liu et al. 2018; Netto et al. 2018) or by initiating neuroinflammation (Fidalgo et al. 2011; reviewed by Skvarc et al. 2018). Additionally, anesthetics and surgery can increase pro-inflammatory cytokine particularly interleukin-6 (IL-6) level in mice (Wu et al. 2012; Shen et al. 2013; Tao et al. 2014; Dong et al. 2016), and IL-6 antibody improved the peripheral surgical wounding-induced cognitive impairment in the aged wild-type mice by comparison to IL-6 knockout mice (Dong et al. 2016). By comparing the inflammatory responses between two type of anesthesia, Mejía-Terrazas et al. showed, in a recent clinical study, that cytokines increased after arthroscopic shoulder surgery but this increase was lower in patients exposed to ultrasound-guided single-dose interscalene block (a novel regional technique for anesthesia or analgesia) compared with the use of balanced general anesthesia (Mejía-Terrazas et al. 2019). Other investigations, demonstrated that the use of non-steroidal anti-inflammatory drugs can prevent the anesthesia and surgery-associated memory deficits probably via their pain-alleviating effects (Shen et al. 2013; Kawano et al. 2014). In the same perspective, curcumin, an active ingredient of plant *Curcuma longa*, is apparently effective in treating POP related to GA and surgery in human (Agarwal et al. 2011; Maulina et al. 2018), and in mice (Sahbaie et al. 2014). As well as suppressing of neuro-inflammatory activation associated with neurodegenerative diseases (Sundaram et al. 2017), and preventing anesthetics exposure-induced POCD in mice (Ji et al. 2015; Wu et al. 2017). The effects of curcumin were probably prompted by enhancing the anti-oxidant enzyme activity, and activation of BDNF (Wu et al. 2017). Furthermore, berberine, an isoquinoline alkaloid from different plants, with anti-inflammatory effects (Li et al. 2019), improved surgery-induced cognitive impairment in aged mice (Zhang et al. 2016).

Moreover, by inducing their effect, anesthesia interferes with a number of neurotransmitters, particularly, the inhibitory γ -aminobutyric acid (GABA) and the excitatory amino acid, glutamate. In this study, the GA was induced by propofol in combination with fentanyl and esmeron. It is known that propofol is an agonist of the inhibitory neurotransmitter GABA by activating GABAA receptor (Irifune et al. 2003) and antagonising excitatory amino acid receptors (Irifune et al. 2003; Wang et al. 2011; Chen et al. 2019). Exposure to propofol during pregnancy downregulates NMDA receptor expression and impairs neuronal development of offspring of rats (Chen et al. 2019). In addition, as it is known that glutamate and its NMDA receptor are involved in learning, memory, and pain (for review, see Qiu et al., 2011; Hardingham

and Bading, 2010; Zhou and Sheng, 2013, Chi et al. 2013; Saffarpour et al. 2017), treatment with memantine, which is an uncompetitive antagonist at glutamatergic NMDA receptors (Reviewed by Kishi et al. 2017) and also a local anesthetic (Chen et al. 2011), reduced the time of recovery, ameliorated the cognitive functions, and reduced POP in rats after anesthesia (Emik et al. 2016; Almahozi et al. 2019). Memantine is also able to protect aged human from POCD after cardiac surgery (Ghaffary et al. 2017).

Another finding of our study was that disturbed patients (NS), following surgery, showed worse cognitive performance (48.4%) than calm patients (66.7%). This outcome is in concordance with the earlier observation of Kain and co-workers that, anxious children during the induction of anesthesia increased their likelihood of developing postoperative negative behavioral changes (Kain et al. 1999; 2004). As well as the finding that adult patient aged more than 18 years, with postoperative agitation after GA were at high risk of postoperative delirium (Fields et al. 2018).

In this study, we have also evaluated the effect of other factors such as: the gender, age, environmental living (rural or urban), schooling (attending school or not), pre-anesthetic consultation (with or without), and the type of intervention (urgent, scheduled or ambulatory). There were no statistical differences between the two groups regarding all these factors and they did not influence the cognitive performance of patients of the two groups.

Conclusion

Our study showed that the use of LRA compared with the use of GA is associated with better postoperative analgesia and better cognitive performance. Postoperative pain, agitation and disturbance of patients were associated with worse cognitive performance.

Abbreviations

Analysis of variance

ANOVA

Brain-derived neurotrophic factor

BDNF

Conditional Associative learning Morocco

CALM

CI

Confidence Interval

Food and Drug Administration

FDA

γ -aminobutyric acid

GABA

γ -aminobutyric acid of type A

GABAA
General anesthesia
GA

Declarations

Ethics approval and consent to participate

Written consent was obtained for each patient from the parent, while verbal consent was obtained from the teenager participant. Indeed the study was conducted according to the guidelines and recommendation of the local ethical committee. The local ethical committee and national regulation regarding the ethical approval are complying with the international standards including the National institute of Health (USA) standards.

Ethics approval and consent to participate

The local ethical committee named “Le comité d’éthique hospitalo-universitaire de Fez” *belonging to the University Hospital of Fez* has processed and approved to conduct this study (*No reference number is applied to such request*).

Consent for publication

All authors are consent to publish this paper

Availability of data and material

Data and materials are available upon request

Competing interests

No competition of interest to declare

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Authors' contributions

JE: data acquisition, evaluation, discussion

AD: Discussion, drafting, data evaluation

EC: data analysis, statistical analysis

SB: data acquisition, evaluation, discussion

MAB: data acquisition, evaluation, discussion

MH: data acquisition, evaluation, discussion

SB: concept, design, follow-up, first draft evaluation

Authors statement

All authors have read and approved the manuscript

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Tables

Table 1

Inclusion and exclusion Criteria of the randomly participating patients in the test.

Inclusion criteria:	Exclusion criteria:
<ul style="list-style-type: none"> • Child between 10 and 15 years old. • Admitted patient at the University Hospital of Fez, cooperating, peaceful and to undergo anesthesia, whatever either general or locoregional; • give consent and the consent of these parents; • patient operated on infant surgery block, CHU Hassan II fez; • child with birth and normal psychomotor development; • No significant pathological history 	<ul style="list-style-type: none"> Children under 10 years, non-patient; - agitated and disturbed children; - Children reported having a history of order diseases psychiatric, psychological or neurological as well as children under treatment for any other disease of the same kind; - Antecedent of head trauma; - Patients followed for a neoplastic pathology, malformation (cardiac, neurological, poly-malformation...); - Children refusing to participate in the study. - Children operated outside infant surgery block, University Hospital of Fez.

Table 2

Distribution of patients by age

Age (years old)	10	11	12	13	14	15
%	17.2	15.6	12.5	17.2	17.2	20.3

Table 3
Data of the univariate statistical analysis in both studied groups.

Factors		General anesthesia	Locoregional anesthesia	p values
Age		12.65%	12.69%	0.26
Gender	Male	33.3%	58.1%	0.91
	Female	66.7%	41.9%	
Environmental living	Rural	40.6%	43.8%	0.67
	Urban	59.4%	56.3%	
Schooling	Attending school	96.9%	93.8%	0.27
	Not attending school	3.1%	6.3%	
Pre-anesthetic consultation	With	53.1%	37.5%	0.07
	Without	46.9%	62.5%	
Type of intervention	Urgent	18.8%	28.1%	0.23
	Scheduled	53.1%	34.4%	
	Ambulatory	28.1%	37.5%	
Postoperative pain (POP)	VAS < 3	34.4%	84.4%	0.02
	VAS ≥ 3	65.6%	15.6%	
Neurological state (NS)	Agitated	75.0%	21.9%	0.02
	Calm	25.0%	78.1%	

Table 4
Results of the descriptive statistical analysis of CALM test.

Performance Factors		Performing patients	Not performing patients	p values
Age (year's old)	10	36.4%	63.6%	0.13
	11	60%	40%	
	12	62.5%	37.5%	
	13	60%	40%	
	14	45.5%	54.5%	
	15	78.6%	21.4%	
Type of anesthesia	General	34.4%	65.6%	0.01
	Locoregional	81.3%	18.8%	
Gender	Male	62.8%	37.2%	0.91
	Female	47.6%	52.4%	
Environmental Living	Rural	55.6%	44.4%	0.67
	Urban	59.5%	40.5%	
Schooling	Yes	67%	41.0%	0.27
	No	33%	59.0%	
Pre-anesthetic consultation	With	51.7%	48.3%	0.23
	Without	34.3%	65.7%	
Type of intervention	Urgent	60%	40%	0.23
	Scheduled	46.4%	53.6%	
	Ambulatory	71.4%	28.6%	
Postoperative pain	Wake up VAS < 3	68.4%	31.6%	0.02
	Wake up VAS ≥ 3	42.3%	57.7%	
Neurological state	Agitated	48.4%	51.6%	0.02
	Calm	66.7%	33.3%	

Table 5
Data of the multivariate statistical analysis in both studied groups.

	OR	(IC 95%)	p-values
Gender	1.534	(0.533–1.412)	0.427
schooling	3.083	(0.267–35.903)	0.369
Type of intervention	0.469	(0.111–1.980)	0.303
Environment	1.008	(0.367–2.768)	0.987
Anesthetic opinion	0.428	(0.154–1.186)	0.780
VAS score	13.176	(2.965–58.545)	0.01
Neurological status	0.74	(0.018–0.310)	0.02
Type of anesthesia	0.12	(0.01–0.0434)	0.01
OR: Odds ratio			
CI: Confidence Interval			
VAS: Visual Analogue Scale (for pain)			