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

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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.)
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 ≥ 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 I 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 sowed 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, Zywieł 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 (Zywiel 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 not 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
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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**References**

Agarwal KA, Tripathi CD, Agarwal BB, Saluja S. Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: a double-blind, randomized placebo-controlled study. SurgEndosc. 2011; 25(12): 3805-3810.

Almahozi A, Radhi M, Alzayer S, Kamal A. Effects of Memantine in a Mouse Model of Postoperative Cognitive Dysfunction. BehavSci (Basel). 2019; 9(3): 24

Aun CS, McBride C, Lee A, Lau AS, Chung RC, Yeung CK, Lai KY, Gin T. Short-Term Changes in Postoperative Cognitive Function in Children Aged 5 to 12 Years Undergoing General Anesthesia: A Cohort Study. Medicine (Baltimore). 2016; 95(14): e3250.

Backeljauw B, Holland SK, Altaye M, Loepke AW. Cognition and brain structure following early childhood surgery with anesthesia. Pediatrics. 2015; 136(1):e1-12.

Bai X, Yan Y, Canfield S, Muravyeva MY, Kikuchi C, et al. (2013) Ketamine enhances human neural stem cell proliferation and induces neuronal apoptosis via reactive oxygen species-mediated mitochondrial pathway. AnesthAnalg 116: 869-880.

Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet. 2009; 12(3): 246-253.

Boscolo A, Milanovic D, Starr JA, Sanchez V, Oklopcic A, Moy L, Ori CC, Erisir A, Jevtovic-Todorovic V (2013) Early exposure to general anesthesia disturbs mitochondrial fission and fusion in the developing rat brain. Anesthesiology 118:1086-1097.

Brambrink AM, Back SA, Riddle A, Gong X, Moravec MD, Dissen GA, Creeley CE, Dikranian KT, Olney
JW. Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. Ann Neurol. 2012; 72:525-535.

Cao SE, Tian J, Chen S, Zhang X, Zhang Y. Role of mir-34c in ketamine-induced neurotoxicity in neonatal mice hippocampus. Cell Biol Int. 2015; 39:164-168.

Chen D, Qi X, Zhuang R, Cao J, Xu Y, Huang X, Li Y. Prenatal propofol exposure downregulates NMDA receptor expression and causes cognitive and emotional disorders in rats. Eur J Pharmacol. 2019; 843: 268-276.

Chen YW, Chu CC, Chen YC, Wang JJ, Hung CH. The local anesthetic effect of memantine on infiltrative cutaneous analgesia in the rat. Anesth Analg. 2011; 113(1): 191-195.

Chi H, Kawano T, Tamura T, Iwata H, Takahashi Y, Eguchi S, Yamazaki F, Kumagai N, Yokoyama M. Postoperative pain impairs subsequent performance on a spatial memory task via effects on N-methyl-D-aspartate receptor in aged rats. Life Sci. 2013; 93: 986-993.

Culley DJ, Cotran EK, Karlsson E, Palanisamy A, Boyd JD, Xie Z, Crosby G. Isoflurane affects the cytoskeleton but not survival, proliferation, or synaptogenic properties of rat astrocytes in vitro. Br J Anaesth. 2013; 110(Suppl 1):i19-28.

Dalla Massara L, Osuru HP, Oklopcic A, Milanovic D, Joksimovic SM, Caputo V, DiGruccio MR, Ori C, Wang G, Todorovic SM, Jevtovic-Todorovic V. General Anesthesia Causes Epigenetic Histone Modulation of c-Fos and Brain-derived Neurotrophic Factor, Target Genes Important for Neuonal Development in the Immature Rat Hippocampus. Anesthesiology. 2016; 124(6):1311-1327.

Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, Hardy P, Hunt RW, Takagi MJ, Giribaldi G, Hartmann PL, Salvo I, Morton NS, von Ungern Sternberg BS, Locatelli BG, Wilton N, Lynn A, Thomas JJ, Polaner D, Bagshaw O, Szmuk P, Absalom AR, Frawley G, Berde C, Ormond GD, Marmor J, McCann ME; GAS consortium. Neurodevelopmental outcome at 2 years of age after general anesthesia and awake-regional anesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet. 2016; 387(10015): 239-50.

DiMaggio C, Sun LS, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. Anesth Analg. 2011; 113(5): 1143-51.
Dong Y, Xu Z, Huang L, Zhang Y, Xie Z. Peripheral surgical wounding may induce cognitive impairment through interleukin-6-dependent mechanisms in aged mice. Med Gas Res. 2016; 6(4):180-186.

Edwards DA, Shah HP, Cao W, Gravenstein N, Seubert CN, Martynyuk AE (2010) Bumetanide alleviates epileptogenic and neurotoxic effects of sevoflurane in neonatal rat brain. Anesthesiology 112:567-575.

Emik U, Unal Y, Arslan M, Demirel CB. The effects of memantine on recovery, cognitive functions, and pain after propofol anesthesia. Braz J Anesthesiol. 2016; 66(5): 485-91.

FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. 2016. Available from http://www.fda.gov/drugs/drugsafety/ucm532356.htm (accessed 8 January 2017)

Fidalgo AR, Cibelli M, White JP, Nagy I, Maze M, Ma D. Systemic inflammation enhances surgery-induced cognitive dysfunction in mice. Neurosci Lett. 2011; 498: 63-66.

Fields A, Huang J, Schroeder D, Sprung J, Weingarten T. Agitation in adults in the post-anesthesia care unit after general anesthesia. Br J Anaesth. 2018; 121(5):1052-1058.

Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics. 2011; 128(5):e1053-61.

Fredriksson A, Ponten E, Gordh T, Eriksson P. Neonatal exposure to a combination of N-methyl-d-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology.2007;107:427-436.

Ghaffary S, Ghaeli P, Talasaz AH, Karimi A, Noroozian M, Salehiomran A, Jalali A. Effect of memantine on post-operative cognitive dysfunction after cardiac surgeries: a randomized clinical trial. Daru. 2017; 25(1): 24.

Glatz P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F. Association of Anesthesia and Surgery During Childhood With Long-term Academic Performance. JAMA Pediatr. 2017; 171(1): e163470.
Hardingham GE, Bading H. Synaptic versus extra synaptic NMDA receptor signaling: implications for neurodegenerative disorders. Nat Rev Neurosci. 2010; 11: 682-696.

Higgins DM, Martin AM, Baker DG, Vasterling JJ, Risbrough V. The Relationship Between Chronic Pain and Neurocognitive Function: A Systematic Review. Clin J Pain. 2018; 34(3):262-275.

Huang C, Zhang X, Zheng J, Chen C, Chen Y, et al. Upregulation of mir-137 protects anesthesia-induced hippocampal neurodegeneration. Int J Clin Exp Pathol. 2014; 7:5000-5007.

Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, Tenkova TI, Stefovska V, Turski L, Olney JW. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999; 283(5398): 70-74.

Irifune M, Takarada T, Shimizu Y, Endo C, Katayama S, Dohi T, Kawahara M. Propofol-induced anesthesia in mice is mediated by gamma-aminobutyric acid-A and excitatory amino acid receptors. Anesth Analg. 2003; 97(2): 424-429.

Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003; 23(3): 876-882.

Ji MH, Qiu LL, Yang JJ, Zhang H, Sun XR, Zhu SH, Li WY, Yang JJ. Pre-administration of curcumin prevents neonatal sevoflurane exposure-induced neurobehavioral abnormalities in mice. Neurotoxicology. 2015; 46: 155-64.

Jiang XL, Du BX, Chen J, Liu L, Shao WB, et al. Microrna-34a negatively regulates anesthesia-induced hippocampal apoptosis and memory impairment through fgfr1. Int J Clin Exp Pathol. 2014; 7:6760-6767.

Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, Feng R, Zhang H. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. 2004; 99(6):1648-1654

Kain ZN, Wang SM, Mayes LC, Caramico LA, Hofstadter MB. Distress during the induction of anesthesia and postoperative behavioral outcomes. Anesth Analg. 1999; 88(5):1042-1047.

Kawano T, Takahashi T, Iwata H, Morikawa A, Imori S, Waki S, Tamura T, Yamazaki F, Eguchi S,
Kumagai N, Yokoyama M. Effects of ketoprofen for prevention of postoperative cognitive dysfunction in aged rats. J Anesth. 2014; 28(6): 932-936.

Kishi T, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. J Alzheimers Dis. 2017; 60(2): 401-425.

Kreth S, Hübner M, Hinske LC. MicroRNAs as Clinical Biomarkers and Therapeutic Tools in Perioperative Medicine. Anesth Analg. 2018; 126(2): 670-681.

Li CL, Tan LH, Wang YF, Luo CD, Chen HB, Lu Q, Li YC, Yang XB, Chen JN, Liu YH, Xie JH, Su ZR. Comparison of anti-inflammatory effects of berberine, and its natural oxidative and reduced derivatives from Rhizoma Coptidis in vitro and in vivo. Phytomedicine. 2019; 52:272-283.

Li L, Liu X, Herr K, Lm RN. Postoperative pain intensity assessment: a comparison of four scales in Chinese adults. Pain Med. 2007; 8(3): 223-234.

Lin D, Liu J, Kramberg L, Ruggiero A, Cottrell J, Kass IS. Early-life single-episode sevoflurane exposure impairs social behavior and cognition later in life. Brain Behav. 2016; 6(9): e00514.

Liu Z, Liu F, Liu X, Ma C, Zhao J. Surgical incision induces learning impairment in mice partially through inhibition of the brain-derived neurotrophic factor signaling pathway in the hippocampus and amygdala. Mol Pain. 2018; 14: 1744806918805902.

Maulina T, Diana H, Cahyanto A, Amaliya A. The efficacy of curcumin in managing acute inflammation pain on the post-surgical removal of impacted third molars patients: A randomised controlled trial. J Oral Rehabil. 2018; 45(9): 677-683.

McCann ME, de Graaff JC, Dorris L, Disma N, Withington D, Bell G, Grobler A, Stargatt R, Hunt RW, Sheppard SJ, Marmor J, Giribaldi G, Bellinger DC, Hartmann PL, Hardy P, Frawley G, Izzo F, von Ungern Sternberg BS, Lynn A, Wilton N, Mueller M, Polaner DM, Absalom AR, Szmuk P, Morton N, Berde C, Soriano S, Davidson AJ; GAS Consortium. Neurodevelopmental outcome at 5 years of age after general anesthesia or awake-regional anesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. Lancet. 2019; 393(10172): 664-677.

Mejía-Terrazas GE, Ruíz-Suárez M, Vadillo-Ortega F, Franco Y Bourland RE, López-Muñoz E. Effect of interscalene nerve block on the inflammatory response in shoulder surgery: a randomized trial. J
Shoulder Elbow Surg. 2019; 28(9):e291-e303.

Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Prog Neurobiol. 2011; 93(3): 385-404.

Netto MB, de Oliveira Junior AN, Goldim M, Mathias K, Fileti ME, da Rosa N, Laurentino AO, de Farias BX, Costa AB, Rezin GT, Fortunato JJ, Giustina AD, Barichello T, Dal-Pizzol F, Petronilho F. Oxidative stress and mitochondrial dysfunction contributes to postoperative cognitive dysfunction in elderly rats. Brain Behav Immun. 2018; 73: 661-669.

O'Farrell RA, Foley AG, Buggy DJ, Gallagher HC. Neurotoxicity of Inhalation Anesthetics in the Neonatal Rat Brain: Effects on Behavior and Neurodegeneration in the Piriform Cortex. Anesthesiol Res Pract. 2018; 2018: Article ID 6376090, 9 pages.

Paule MG, Li M, Allen RR, Liu F, Zou X, Hotchkiss C, et al. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. NeurotoxicolTeratol. 2011; 33(2): 220-230.

Qiu S, Li XY, Zhuo M. Post-translational modification of NMDA receptor GluN2B subunit and its roles in chronic pain and memory. Semin Cell Dev Biol. 2011; 22: 521-529.

Rudin M, Ben-Abraham R, Gazit V, Tendler Y, Tashlykov V, Katz Y. Single-dose ketamine administration induces apoptosis in neonatal mouse brain. J Basic ClinPhysiolPharmacol. 2005;16(4):231-43.

Ryu YK, Khan S, Smith SC, Mintz CD. Isoflurane impairs the capacity of astrocytes to support neuronal development in a mouse dissociated coculture model. J Neurosurgical Anesth.2014; 26:363-368.

Saffarpour S, Shaabani M, Naghdi N, Farahmandfar M, Janzadeh A, Nasirinezhad F. In vivo evaluation of the hippocampal glutamate, GABA and the BDNF levels associated with spatial memory performance in a rodent model of neuropathic pain. PhysiolBehav. 2017; 175:97-103.

Sahbaie P, Sun Y, Liang DY, Shi XY, Clark JD. Curcumin treatment attenuates pain and enhances functional recovery after incision. AnesthAnalg. 2014; 118(6): 1336-1344.

Sall JW, Stratmann G, Leong J, McKleroy W, Mason D, Shenoy S, et al. Isoflurane inhibits growth but does not cause cell death in hippocampal neural precursor cells grown in culture. Anesthesiology.
Sanchez V, Feinstein SD, Lunardi N, Jokovic PM, Boscolo A, Todorovic SM, et al. General anesthesia causes long-term impairment of mitochondrial morphogenesis and synaptic transmission in developing rat brain. Anesthesiology 2011;115(5):992-1002.

Schneuer FJ, Bentley JP, Davidson AJ, Holland AJ, Badawi N, Martin AJ, Skowno J, Lain SJ, Nassar N. The impact of general anesthesia on child development and school performance: a population-based study. Paediatr Anaesth. 2018; 28(6): 528-536.

Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, Sun D, Baxter MG, Zhang Y, Xie Z. Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. Anesthesiology. 2013; 118(3):502-515.

Skvarc DR, Berk M, Byrne LK, Dean OM, Dodd S, Lewis M, Marriott A, Moore EM, Morris G, Page RS, Gray L. Post-Operative Cognitive Dysfunction: An exploration of the inflammatory hypothesis and novel therapies. Neurosci Biobehav Rev. 2018; 84:116-133.

Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanić K, Welch TL, Olson MD, Hanson AC, Schroeder DR, Wilder RT, Warner DO. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin. Proc. 2012, 87, 120-129.

Sun LS, Li G, Miller TL, Salorio C, Byrne MW, Bellinger DC, Ing C, Park R, Radcliffe J, Hays SR, DiMaggio CJ, Cooper TJ, Rauh V, Maxwell LG, Youn A, McGowan FX. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA. 2016; 315: 2312-2320.

Sundaram JR, Poore CP, Sulaimee NHB, Pareek T, Cheong WF, Wenk MR, Pant HC, Frautschy SA, Low CM, Kesavapany S. Curcumin Ameliorates Neuroinflammation, Neurodegeneration, and Memory Deficits in p25 Transgenic Mouse Model that Bears Hallmarks of Alzheimer's Disease. J Alzheimers Dis. 2017; 60(4):1429-1442.

Takadera T, Ishida A, Ohyashiki T. Ketamine-induced apoptosis in cultured rat cortical neurons. Toxicol Appl Pharmacol. 2006; 210: 100-107.

Tao G, Zhang J, Zhang L, Dong Y, Yu B, Crosby G, Culley DJ, Zhang Y, Xie Z. Sevoflurane induces tau
phosphorylation and glycogen synthase kinase 3beta activation in young mice. Anesthesiology (2014) 121(3):510-527.

Twaroski DM, Yan Y, Olson JM, Bosnjak ZJ, Bai X. Down-regulation of microrna-21 is involved in the propofol-induced neurotoxicity observed in human stem cell-derived neurons. Anesthesiology. 2014; 121:786-800.

Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M. Postoperative impairment of cognitive function in rats: A possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology. 2007; 106: 436-443.

Wang C, Sadovova N, Hotchkiss C, Fu X, Scallet AC, Patterson TA, Hanig J, Paule MG, Slikker W Jr. Blockade of N-methyl-D-aspartate receptors by ketamine produces loss of postnatal day 3 monkey frontal cortical neurons in culture. Toxicol Sci. 2006; 91(1):192-201.

Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM. The effects of postoperative pain and its management on postoperative cognitive dysfunction. Am J Geriatr Psychiatry. 2007; 15(1): 50-59.

Wang X, Yang Y, Zhou X, Wu J, Li J, Jiang X, Qu Q, Ou C, Liu L, Zhou S. Propofol pretreatment increases antidepressant-like effects induced by acute administration of ketamine in rats receiving forced swimming test. Psychiatry Res. 2011; 185(1-2): 248-53.

Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009; 110(4): 796-804.

Wu J, Bie B, Naguib M (2016) Epigenetic manipulation of brain-derived neurotrophic factor improves memory deficiency induced by neonatal anesthesia in rats. Anesthesiology 124:624-640.

Wu X, Chen H, Huang C, Gu X, Wang J, Xu D, Yu X, Shuai C, Chen L, Li S, Xu Y, Gao T, Ye M, Su W, Liu H, Zhang J, Wang C, Chen J, Wang Q, Cui W. Curcumin attenuates surgery-induced cognitive dysfunction in aged mice. Metab Brain Dis. 2017; 32(3): 789-798.

Wu X, Lu Y, Dong Y, Zhang G, Zhang Y, Xu Z, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-alpha, IL-6, and IL-1beta. Neurobiol Aging (2012) 33(7): 1364-1378.
Xiao H, Liu B, Chen Y, Zhang J. Learning, memory and synaptic plasticity in hippocampus in rats exposed to sevoflurane. Int J Dev Neurosci. 2016; 48: 38-49.

Xie SN, Ye H, Li JF, An LX. Sevoflurane neurotoxicity in neonatal rats is related to an increase in the GABA(A) R α1/GABA(A) R α2 ratio. J Neurosci Res. 2017; 95(12): 2367-2375.

Xu H, Zhang J, Zhou W, Feng Y, Teng S, Song X. The role of mir-124 in modulating hippocampal neurotoxicity induced by ketamine anaesthesia. Int J Neurosci. 2015; 125(3): 213-220.

Xu Z, Dong Y, Wang H, Culley DJ, Marcantonio ER, Crosby G, Tanzi RE, Zhang Y, Xie Z. Peripheral surgical wounding and age-dependent neuroinflammation in mice. PLoS One (2014) 9(5):e96752.

Yu D, Jiang Y, Gao J, Liu B, Chen P (2013) Repeated exposure to propofol potentiates neuroapoptosis and long-term behavioral deficits in neonatal rats. NeurosciLett 534: 41-46

Zhang Q, Peng Y, Wang Y. Long-duration general anesthesia influences the intelligence of school age children. BMC Anesthesiol. 2017; 17(1):170.

Zhang S, Dong H, Zhang X, Li N, Sun J, Qian Y. Cerebral mast cells contribute to postoperative cognitive dysfunction by promoting blood brain barrier disruption. Behav Brain Res (2016) 298(Pt B):158-66.

Zhang X, Xin X, Dong Y, Zhang Y, Yu B, Mao J, Xie Z. Surgical incision-induced nociception causes cognitive impairment and reduction in synaptic NMDA receptor 2B in mice. J Neurosci 2013; 33: 17737-17748.

Zhang Y, Dong Y, Wu X, Lu Y, Xu Z, et al. (2010). The mitochondrial pathway of anesthetic isoflurane-induced apoptosis. J Biol Chem 285: 4025-4037.

Zhao X, Jin Y, Li H, Jia Y, Wang Y. Sevoflurane impairs learning and memory of the developing brain through post-transcriptional inhibition of CCNA2 via microRNA-19-3p. Aging (Albany NY). 2018; 10(12): 3794-3805.

Zhou B, Chen L, Liao P, Huang L, Chen Z, Liao D, Yang L, Wang J, Yu G, Wang L, Zhang J, Zuo Y, Liu J, Jiang R. Astroglial dysfunctions drive aberrant synaptogenesis and social behavioral deficits in mice with neonatal exposure to lengthy general anesthesia. PLoS Biol. 2019; 17(8):e3000086.

Zhou Q, Sheng M. NMDA receptors in nervous system diseases. Neuropharmacology.2013; 74: 69-75.
Zhu C, Gao J, Karlsson N, Li Q, Zhang Y, Huang Z, Li H, Kuhn HG, Blomgren K. Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult, rodents. J Cereb Blood Flow Metab. 2010; 30(5):1017-1030.

Zou X, Patterson TA, Divine RL, Sadovova N, Zhang X, Hanig JP, et al. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci 2009; 27:727-31.

Zywiel MG, Prabhu A, Perruccio AV, Gandhi R. The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: a systematic review. Clin Orthop Relat Res. 2014; 472(5): 1453-66.

Tables

| Table 1 |
|-------------------------------|-------------------------------|
| **Inclusion and exclusion Criteria of the randomly participating patients in the test.** | |
| **Inclusion criteria:** | **Exclusion criteria:** |
| • Child between 10 and 15 years old. | Children under 10 years, non-patient; |
| • Admitted patient at the University Hospital of Fez, cooperating, peaceful and to undergo anesthesia, whatever either general or locoregional; | - agitated and disturbed children; |
| • give consent and the consent of these parents; | - 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; |
| • patient operated on infant surgery block, CHU Hassan II fez; | - Antecedent of head trauma; |
| • child with birth and normal psychomotor development; | - Patients followed for a neoplastic pathology, malformation (cardiac, neurological, poly-malformation...); |
| • No significant pathological history | - 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     |
| Gender                         | Female 66.7%       | 41.9%                   |          |
| Environmental living           | Rural 40.6%        | 43.8%                   | 0.67     |
| Environmental living           | Urban 59.4%        | 56.3%                   |          |
| Schooling                      | Attending school 96.9% | 93.8%                  | 0.27     |
| Schooling                      | Not attending school 3.1% | 6.3%                   |          |
| Pre-anesthetic consultation    | With 53.1%         | 37.5%                   | 0.07     |
| Pre-anesthetic consultation    | Without 46.9%      | 62.5%                   |          |
| Type of intervention           | Urgent 18.8%       | 28.1%                   | 0.23     |
| Type of intervention           | Scheduled 53.1%    | 34.4%                   |          |
| Type of intervention           | Ambulatory 28.1%   | 37.5%                   |          |
| Postoperative pain (POP)       | VAS < 3 34.4%      | 84.4%                   | 0.02     |
| Postoperative pain (POP)       | VAS ≥ 3 65.6%      | 15.6%                   |          |
| Neurological state (NS)        | Agitated 75.0%     | 21.9%                   | 0.02     |
| Neurological state (NS)        | 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%                   |          |
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)