UNIVERSIDAD DE MURCIA

ESCUELA INTERNACIONAL DE DOCTORADO

TESIS DOCTORAL

Hemodynamic, ventilatory and BIS monitoring changes in Pediatric Dentistry

Cambios hemodinámicos, ventilatorios y de la monitorización con BIS en Odontología pediátrica

D.ª Silvia Pérez García

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UNIVERSIDAD DE MURCIA

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Hemodynamic, ventilatory and BIS monitoring changes in Pediatric Dentistry

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A mi abuelo Pepe, aquel día y aquella mirada me acompaña y me da fuerzas cada día.

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Summary

This Doctoral Thesis is a compendium of three publications in scientific journals of the *Journal Citation Reports* (JCR) (Clarivate, Chandler, AZ, USA) (*Medicina Oral Patología Oral Cirugía Bucal, Journal of Clinical and Experimental Dentistry and Special Care in Dentistry*) seeking to broaden our knowledge and understanding of the hemodynamic, ventilatory and BIS changes that occur during dental treatment in pediatric patients.

Patient stress due to dental procedures is often related to a sense of fear, anxiety and uncertainty. The mental and physical stress that occurs during dental treatment often triggers cardiovascular changes. The use of non-pharmacological management strategies is unable to resolve resistive and uncooperative behavior, especially in children under three years of age or with special needs. In these cases, patients require additional support such as sedation or general anesthesia (GA), beyond local anesthesia (LA), in order to receive dental treatment.

Monitoring of sedation and GA can be broadly divided into the monitoring of cardiorespiratory function and monitoring of the depth of sedation / GA. In current practice, these two aspects are not separate, however. Cardiorespiratory function is monitored clinically and by using pulsioximetry to monitor oxygen saturation and pulse rate, with the use of a blood pressure cuff to monitor blood pressure. The depth of sedation or GA is usually monitored through clinical observation of the patient and by applying some sedation criterion such as Verrill's sign (partial drooping of the eyelids), patient movement, asking the patient if he/she feels relaxed or not, or employing different sedation assessment scales (the most popular being the Observer's Assessment of Alertness and Sedation Scale [OAA/S], the University of Michigan Sedation Scale [UMSS] and the Ramsay Sedation Scale). However, since these are subjective methods, differences in clinical interpretation may lead to inter- and intra-operator variability and a lack of reliability and

consistency - potentially resulting in inaccurate judgment of the depth of sedation and its consequences.

Firstly, a systematic review published in *Medicina Oral Patología Oral y Cirugía Bucal* was carried out. The aim of this systematic review was to evaluate the use of bispectral index (BIS) monitoring during intravenous sedation in patients undergoing dental treatment, comparing BIS versus sedation scales. Electroencephalography (EEG) can also be used to assess the depth of sedation, providing an objective evaluation of the suppression of the central nervous system, but it is difficult to interpret clinically. Bispectral index monitoring involves a complex mathematical calculation of EEG data, and is directly related to cortical activity in which the shape of EEG waves changes with the patient's level of alertness. The BIS is a scale from 100 to 0, where values over 90 indicate that the patient is awake, and 70 to 90 indicates light to moderate sedation. Deep sedation is in the range of 60 to 70, and GA corresponds to values of 40 to 60. In turn, a BIS value of under 40 is indicative of a deep hypnotic state, and 0 represents total electrical silence (complete cortical suppression).

This review showed that with the use of BIS for sedation monitoring, it is possible to evaluate sedation levels objectively in real time, eliminating the need for clinical evaluation. This is particularly important in the field of dentistry, where the presence of intraoral instruments makes it difficult to assess patient facial expression and establish communication to assess the level of sedation. In addition, the use of BIS monitoring reduces the need for intravenous sedation drugs, lessening the probability of side effects and reducing the economic cost of the procedures. However, according to some authors, the use of BIS in dentistry remains subject to controversy. One of the main reasons for this is that the sensor of the monitoring device is placed on the forehead of the patient, close to the operating area. As a result, it is easy to provoke interferences in muscular activity or distortion of the BIS readings as a result of the use of high-frequency electrical apparatuses.

The BIS monitoring of conscious sedation offers better safety, particularly when intravenous sedation techniques are applied in a non-hospital operating room setting. Nevertheless, further research within the field of dentistry is needed to confirm these advantages and overcome the limitations identified in the works analyzed in this review.

As previously mentioned, patients with special needs require additional support beyond local anesthesia, in order to receive dental treatment.

While conscious and moderate sedation often suffices for performing most dental treatments in adults, deeper sedation levels or even GA may occasionally be required in children under 7 years of age and in patients with special needs.

For the second and third works we had the approval of the Ethics Committee of the Faculty of Dentistry of the University of Murcia (Murcia, Spain) (Committee registry number 1459-2017).

The second paper, published in the *Journal of Clinical and Experimental Dentistry*, focuses on this group of patients with special needs. Although the literature on the use of BIS in dentistry is increasing, the majority of studies have been conducted in adults, and the data referred to adults might not be applicable to the pediatric population. Furthermore, the literature offers very limited data on the validity of BIS monitoring in the case of children with systemic diseases or with neuronal disorders, because it is difficult to recruit a sufficient number of subjects belonging to this vulnerable population. Because of this, the purpose of this study was to determine the hemodynamic and ventilatory changes and BIS values after propofol and sevoflurane administration in children with special needs versus healthy children, during dental treatment.

We included 40 uncooperative pediatric patients that were allocated to two groups: a control group of healthy children (HC) and a study group of children with special needs (CSN) according to the classification of Maeda et al. (1)

referred to function, disability and health in relation to the tolerability of dental treatment.

Informed consent was obtained from all parents prior to the investigation, after fully explaining the benefits, inconveniences and potential risks of the intervention.

A pediatric blood pressure cuff was placed on the right arm, a pulsioximetry probe was attached to the index finger of the left hand, and three electrodes for continuous electrocardiogram monitoring were placed.

BIS monitoring was performed using the Covidien BIS Complete Monitoring System® (Covidien Inc., Mansfield, MA, USA) with commercially available pediatric BIS sensor strips.

Sevoflurane in oxygen (100% oxygen, 5 l/min) and continuous propofol infusion (target-controlled infusion [TCI], 2 μg/ml) were used as sedative agents, and 2% lidocaine with 1:80,000 adrenaline was used as local anesthesia in both groups. A flexometallic laryngeal mask (LMA, Proseal® airway, Teleflex Medical Europe, Ltd.) was inserted and fixed on the side opposite to the mouth-opener for continuous oxygen administration (2 l/min), under spontaneous breathing conditions at all times. Heart rate, SaO_2, respiratory rate, CO_2, blood pressure and BIS values were recorded at baseline, the start of treatment, and every 15 minutes during the entire dental procedure. The dental treatments were performed using the usual techniques, and were recorded for each patient. Postoperative instructions were provided, and analgesic and antiemetic medication was prescribed. The parents were called by phone on the same day in the afternoon and again on the following day to assess possible complications.

The most common disorder in the CSN group was autism or autism spectrum disorder (ASD), followed by Down syndrome and chronic encephalopathy.

The mean heart rate and BIS values were lower during treatment in the CSN group than in the HC group. The lowest BIS value observed in the present study corresponded to the CSN group, employing the same dose of anesthetic drug. The lower values possibly could be explained by the fact that some brain disorders may exhibit epileptiform or non-epileptiform forms, or need anticonvulsivant medication.
The variables blood pressure, respiratory rate, SaO_2, and CO_2 behaved slightly differently in the two groups, but there were no statistically significant differences over treatment time.

Although GA is a safe procedure, postoperative dental morbidity or complications have been described. Nevertheless, in our study no intra- or postoperative complications were recorded.

As we have commented, these drugs caused a significant decrease in heart rate and BIS values in children with special needs versus healthy children. Blood pressure, SaO_2 and exhaled carbon dioxide showed similar results in both groups. In conclusion, propofol and sevoflurane administration allows dental treatment to be performed safely in children with special needs who otherwise would not be treated.

For the third paper, published in *Special Care in Dentistry*, we decided to take advantage of the data we had from healthy patients treated under GA to compare their hemodynamic variables versus patients treated only with local LA.

It is known that sedation is associated with a drop in patient blood pressure, which allows dental treatment to be carried out more safely and with a lesser risk of complications. However, fewer data are available on the effect of sevoflurane and propofol upon hemodynamic variables in pediatric patients undergoing dental treatment under GA.

Forty pediatric patients needing dental treatment were assigned to either general anesthesia with local anesthesia (study group [SG]) or local anesthesia

alone (control group [CG]). Two percent sevoflurane in oxygen (100% oxygen, 5 l/min) and continuous propofol infusion (TCI, 2 μg/ml) were used as GA agents in SG as described in the previous paper, and 2% lidocaine with 1:80,000 adrenaline was used as local anesthesia in both groups. Heart rate, blood pressure and SaO_2 were measured before starting dental treatment (baseline) and every 10 minutes during treatment.
Systolic blood pressure, diastolic blood pressure and heart rate decreased substantially after the administration of GA. The levels of these parameters subsequently remained low and then recovered at the end of the procedure. On the other hand, the SaO_2 values remained closer to baseline in SG versus CG. In contrast, the hemodynamic parameters experienced lesser fluctuation in CG than in SG.

Side effects have been described associated to some of the drugs used to perform the GA (hypoxia, nausea, vomiting, tachycardia or allergic reactions). We recorded no side effects during our study. Nevertheless, these may occur during such procedures, and despite the low incidence of adverse outcomes from GA in the dental office setting, anesthesiologists should safely and efficiently complete treatment.

Another aspect to consider is when uncooperative patients are subjected to GA. They require a greater number of dental treatments (many times, and the oral disorders they present are extensive due to delays in visiting the dentist). Given an equal number of treatments to be carried out on a patient, multiple and briefer sessions are preferred in collaborating patients so that they do not get tired and maintain their cooperation.

General anesthesia seems to afford more favorable cardiovascular parameters during the dental treatment process versus LA alone in pediatric patients, showing significant lower systolic and diastolic blood pressure values and heart rate. In addition, GA allows dental treatment to be performed in healthy, uncooperative children who could not be treated with LA alone.

Our studies presented some difficulties and limitations. The available literature on the behavior of cardiopulmonary parameters in dentistry and under GA involving pediatric patients is limited. Recent evidence suggests that parental satisfaction with dental treatment under GA has increased in recent years, and that it is now accepted more favorably than other active or passive behavioral management techniques. Considering the small changes recorded in some of the study parameters, a larger sample size would also be advisable in the context of future investigations.

Resumen

Esta Tesis Doctoral es un compendio de tres publicaciones del *Journal Citation Reports* (JCR) (Clarivate, Chandler, AZ, USA) (*Medicina Oral Patología Oral Cirugía Bucal, Journal of Clinical and Experimental Dentistry and Special Care in Dentistry*) que buscan ampliar nuestro conocimiento y comprensión de los cambios hemodinámicos, ventilatorios y del BIS que se producen durante el tratamiento odontológico en pacientes pediátricos.

El estrés del paciente debido a los procedimientos dentales está a menudo relacionado con una sensación de miedo, ansiedad e incertidumbre. El estrés físico y mental que se produce durante el tratamiento dental suele desencadenar cambios cardiovasculares. El uso de estrategias de manejo de conducta no farmacológico es incapaz de resolver conductas no cooperantes, especialmente en niños menores de tres años o con necesidades especiales. En estos casos, los pacientes requieren un apoyo adicional más allá de la anestesia local, como la sedación o la Anestesia General (AG), para poder recibir el tratamiento odontológico.

La monitorización de la sedación y la Anestesia General la podemos dividir en términos generales en monitorización de la función cardiorrespiratoria y monitorización de la profundización de la sedación/AG. Sin embargo, en la práctica actual estos dos aspectos no están separados. La función cardiorrespiratoria se monitoriza clínicamente mediante la pulsioximetría para controlar la saturación de oxígeno y el pulso, y con el uso de un manguito para la tensión arterial. La profundidad de la sedación o la AG suele monitorizarse mediante la observación clínica del paciente y con el uso de algún criterio clínico de sedación como el signo de Verrill (caída parcial de los párpados), el movimiento del paciente, preguntando al paciente si se siente relajado o no, o empleando diferentes escalas de evalucaicón de la sedación (las más populares son la Escala de Evaluación de Alerta y Sedación del Observador [OAA/S], la Escala de Sedación de la Universidad de Michigan [UMSS] y la Escala de Sedación de Ramsay). Sin embargo, dado que se trata de métodos subjetivos, las diferencias en la interpretación clínica pueden producir

variabilidad entre operadores e intraoperadores y una falta de fiabilidad y coherencia, lo que podría dar lugar a una valoración inexacta de la profundidad de la sedación y sus consecuencias.

En primer lugar se realizó una revisión sistemática publicada en la revista *Medicina Oral Patología Oral y Cirugía Bucal.* El objetivo de esta revisión sistemática fue evaluar el uso de la monitorización con índice biespectral (BIS) durante la sedación endovenosa en pacientes sometidos a tratamiento odontológico, comparando el BIS con las escalas de sedación. La electroencefalografía (EEG) también se puede utilizar para evaluar la profundidad de sedación, dando una valoración objetiva de la supresión del Sistema Nervioso Central, pero es difícil de interpretar clínicamente. La monitorización del BIS implica un cálculo matemático complejo de los datos del EEG y está directamente relacionada con la actividad cortical en la que la forma de las ondas del EEG cambian con el nivel de alerta del paciente. El BIS es una escala de 100 a 0, donde los valores superiores a 90 indican que el paciente está despierto y valores de 70 a 90 indican una sedación de moderada a ligera. La sedación profunda va de 60 a 70 y la AG se corresponde con valores de 40 a 60. Un valor de BIS inferior a 40 es indicativo de un estado hipnótico profundo y 0 representa la ausencia de señal eléctrica (supresión cortical completa).

Esta revisión mostró que con el uso del BIS para la monitorización de la sedación, es posible evaluar los niveles de sedación objetivamente y en tiempo real, eliminando la necesidad de realizar una valoración clínica del paciente. Esto es especialmente importante en el campo de la odontología, donde la presencia de instrumentos intraorales dificulta valorar la expresión facial del paciente, así como la comunicación con él con el fin de evaluar el nivel de sedación. Además, el uso de la monitorización con BIS reduce la necesidad de sedantes intravenosos, disminuyendo la probabilidad de aparición de efectos secundarios y reduciendo el coste económico de los procedimientos. Sin embargo, según algunos autores, el uso del BIS en odontología sigue siendo controvertido. Una de las razones principales es que el sensor del dispositivo se coloca en la frente del paciente, cerca del área de trabajo. Como resultado,

es fácil provocar interferencias en la actividad muscular o también distorsión en las lecturas de los valores del BIS debido al uso de aparatos eléctricos de alta frecuencia.

La monitorización de la sedación consciente con BIS ofrece mayor seguridad, sobretodo cuando las técnicas de sedación endovenosa se aplican en un gabinete dental extrahospitalario. Sin embargo se necesitan más investigaciones dentro del campo de la odontología para confirmar estas ventajas y superar las limitaciones identificadas en los trabajos analizados en esta revisión.

Como se ha mencionado anteriormente, los pacientes con necesidades especiales requieren un apoyo adicional más allá de la anestesia local para poder recibir el tratamiento odontológico.

Si bien la sedación consciente moderada suele ser suficiente para realizar la mayoría de los tratamientos dentales en adultos, en niños menores de 7 años y en pacientes con necesidades especiales pueden ser necesarios niveles de sedación profundos o incluso la AG.

Para el segundo y tercer artículos contamos con la aprobación del Comité de Ética de la Facultad de Odontología de la Universidad de Murcia (Murcia, España) (Número de registro del comité 1459-2017).

El segundo artículo, publicado en el *Journal of Clinical and Experimental Dentistry,* se centra en un grupo de pacientes pediátricos con necesidades especiales. Aunque la literatura científica sobre el uso del BIS en odontología es cada vez más numerosa, la mayoría de los estudios publicados se han realizado en pacientes adultos y estos datos podrían no ser aplicables a la población pediátrica. Además la literatura ofrece datos muy limitados sobe la validez del BIS en el caso de niños con enfermedades sistémicas o con trastornos neuronales, ya que es difícil reclutar el número suficiente de sujetos pertenecientes a esta población vulnerable. Por ello, el objetivo de este estudio fue determinar los cambios hemodinámicos, ventilatorios y los valores del BIS

producidos tras la administración de propofol y sevoflurano en niños con necesidades especiales en comparación con niños sanos, durante el tratamiento odontológico.

Se incluyeron 40 pacientes pediátricos no cooperadores que fueron asignados a dos grupos: un grupo control de niños sanos (HC) y un grupo de estudio de niños con necesidades especiales (CSN) según la clasificación de Maeda et al. (1) referida a la función, discapacidad y salud en relación con la tolerancia al tratamiento dental.

Se obtuvo el consentimiento informado de todos los padres antes de la investigación, tras explicarles detalladamente los beneficios, los inconvenientes y los riesgos potenciales del tratamiento.

Se les colocó un manguito de presión arterial pediátrico en el brazo derecho, se les conectó el pulsioxímetro en el dedo índice de la mano izquierda y se les colocaron tres electrodos para la monitorización continua del electrocardiograma.

La monitorización del BIS se realizó utilizando el Covidien BIS Complete Monitoring System ® (Covidien Inc., Mansfiel, MA, EEUU) con sensores pediátricos.

Los fármacos que se utilizaron en ambos grupos fueron el sevoflurano en oxígeno (oxígeno al 100%, 5 l/min) y propofol en infusión continua (TCI 2µg/ml) y como anestésico local la lidocaína al 2% con adrenalina 1:80000. Se insertó y fijó una mascarilla laríngea flexometálica (LMA, Proseal ® airway, Teleflex Medical Europe, Ltd.) en el lado opuesto al abrebocas para administrar continuamente oxígeno (2 l/min), bajo respiración espontánea. Se registraron la frecuencia cardíaca, saturación de oxígeno, frecuencia respiratoria, CO_2 exhalado, tensión arterial y valores del BIS, en reposo, al inicio del tratamiento y cada 15 minutos durante todo el tratamiento dental. Los tratamientos odontológicos se realizaron mediante las técnicas habituales y se fueron registrando en todos los pacientes. Se dieron las instrucciones postoperatorias

y se prescribió medicación analgésica y antiemética. Se llamó por teléfono a los padres el mismo día de la intervención por la tarde, así como al día siguiente para valorar posibles complicaciones, que en caso de haberlas se registraban en su historia clínica.

El trastorno más común en el grupo CSN fue el autismo o trastorno del espectro autista (TEA), seguido del síndrome de Down y la encefalopatía crónica.

La frecuencia cardíaca media y los valores BIS durante el tratamiento fueron más bajos en el grupo CSN que en el grupo HC. El valor BIS más bajo para una misma dosis de anestésico observado en este estudio correspondió al grupo CSN. Los valores más bajos se podrían explicar posiblemente por el hecho de que algunos trastornos cerebrales pueden presentar formas epileptiformes o no epileptiformes, o necesitar medicación anticonvulsivante.

Las variables tensión arterial, frecuencia respiratoria, SaO_2 y CO_2 expirado se comportan de manera ligeramente diferente en los dos grupos aunque no se observaron diferencias estadísticamente significativas durante el tiempo del tratamiento.

Como se ha comentado con anterioridad, estos fármacos provocaron una disminución significativa de la frecuencia cardíaca y de los valores del BIS en niños con necesidades especiales frente a niños sanos. La tensión arterial, la SaO_2 y el CO_2 exhalado mostraron resultados similares en ambos grupos. En conclusión, la administración de propofol y sevoflurano permite realizar tratamientos odontológicos de forma segura en niños con necesidades especiales que de otro modo no podrían ser tratados.

Para el tercer artículo, publicado en la revista *Special Care in Dentistry,* para el grupo control se utilizaron los datos de los pacientes sanos tratados con AG del segundo artículo, con el fin de comparar sus variables hemodinámicas con las de pacientes sanos tratados solo administrando anestesia local.

La sedación endovenosa se asocia con una bajada de la presión arterial del paciente, lo que permite realizar el tratamiento odontológico de forma más segura y con menor riesgo de complicaciones. Sin embargo, hay menos datos disponibles sobre el efecto del sevoflurano y el propofol sobre las variables hemodinámicas en pacientes pediátricos sometidos a tratamiento odontológico bajo AG.

Cuarenta pacientes con necesidad de tratamiento odontológico fueron divididos en dos grupos, uno con pacientes que necesitaban anestesia general y anestesia local (grupo de estudio [SG]) y otro grupo con aquellos que podían recibir el tratamiento solo con anestesia local (grupo de control [CG]). Para la anestesia general se utilizó sevoflurano al 2% en oxígeno (100% oxígeno, 5 l/min) e infusión continua de propofol (TCI, 2μg/ml) tal y como se describe en el artículo anterior. Como anestesia local se utilizó la lidocaína al 2% con adrenalina 1:80000 en ambos grupos. Se midió la frecuencia cardíaca, la tensión arterial, la SaO_2 antes de empezar el tratamiento y al inicio y cada 10 minutos durante todo el tratamiento dental.

La tensión arterial sistólica, la tensión arterial diastólica y la frecuencia cardíaca disminuyeron sustancialmente después de la administración de la AG. Posteriormente, los niveles de estos parámetros permanecieron bajos para recuperarse al final de procedimiento. Por otro lado, los valores de SaO_2 se mantuvieron cercanos al valor inicial en el SG en relación con el CG. En comparación, los parámetros hemodinámicos experimentaron una menor fluctuación en el CG respecto al SG.

Se han descrito efectos secundarios asociados a algunos de los fármacos utilizados en la AG tales como hipoxia, náuseas, vómitos, taquicardia o reacciones alérgicas. Aunque durante nuestro estudio no se presentaron complicaciones y la literatura describe una baja incidencia, estas pueden producirse en la consulta dental por lo que los anestesistas deben realizar el tratamiento siempre de manera segura y eficaz.

Otro aspecto a considerar es el paciente que no coopera y al que se le somete a una AG, puesto que éstos requieren de un mayor número de tratamientos odontológicos (muchas veces presentan más patología bucal debido al retraso en la visita al odontólogo). Sin embargo, ante un número igual de tratamientos a realizar, en los pacientes colaboradores se prefieren sesiones múltiples y más breves para que estos no se cansen y mantengan en todo momento su colaboración.

En los pacientes pediátricos la anestesia general parece proporcionar parámetros cardiovasculares más favorables durante el tratamiento dental respecto a la anestesia local sola, mostrando valores de tensión arterial sistólica y diastólica y frecuencia cardíaca significativamente más bajos. Además la AG permite realizar tratamientos dentales en niños sanos y que no colaboran que no podrían ser tatados solo con la anestesia local.

Nuestros estudios presentaron algunas dificultades y limitaciones. La literatura disponible sobre el comportamiento de los parámetros cardiopulmonares en odontología bajo AG en pacientes pediátricos es limitada. La evidencia reciente sugiere que la satisfacción de los padres con el tratamiento dental bajo AG ha aumentado en los últimos años y que ahora se acepta más favorablemente que otras técnicas de manejo conductual activo o pasivo. Considerando los pequeños cambios registrados en algunos de los parámetros del estudio, sería aconsejable aumentar el tamaño de la muestra en futuras investigaciones.

List of abbreviations *(in alphabetical order)*

ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
BIS	Bispectral index
BP	Blood pressure
CG	Control group
CO_2	Exhaled carbon dioxide
CSN	Children with special needs
DBP	Diastolic blood pressure
DSTG	Dental Sedation Teachers Group
EEG	Electroencephalography
GA	General anesthesia
HC	Healthy children
HR	Heart rate
LA	Local anesthesia
LMA	Flexometallic laryngeal mask
OAA/S	Observer's Assessment of Alertness and Sedation Scale
RR	Respiratory rate
SBP	Systolic blood pressure
SG	Study group
TCI	Target-controlled infusion
SaO_2	Oxygen saturation
SPSS	Statistical Package for the Social Sciences
UMSS	University of Michigan Sedation Scale

List of Figures and Tables

Figures

Tables

1. List of papers

This thesis is based on three previously published papers, as follows:

Paper I

Evaluation of endovenous sedation using BIS monitoring in dentistry. A systematic review. Pérez-García S, Lozano-Carrascal N, Ruiz-Roca JA, López-Jornet P, Gargallo-Albiol J.
Med Oral Patol Oral Cir Bucal. 2020 Jul 1;25 (4):e439-48.
doi:10.4317/medoral. 22884

Paper II

Hemodynamic and ventilatory changes in pediatric patients with special needs: a comparative clinical study. Pérez-García S, Ruiz-Roca JA, Añez C, López-Jornet P, Gargallo-Albiol J.
J Clin Exp Dent. 2022;14(11):e909-19.
doi:10.4317/jced.59951

Paper III

Comparison of hemodynamic changes with general or local anesthesia during dental treatment in pediatric patients: a prospective clinical study.
Pérez-García S, Acosta-Ibarra J, Ruiz-Roca JA, Añez C, Gargallo-Albiol J.
Spec Care Dentist 2023;1-12
doi: 10.1111/scd.12890

2. Background

Providing dental care for anxious and fearful patients is a major challenge for dentists (2,3). Moreover, in the case of pediatric patients, the dental visit can represent a shocking event (4).

Anxiety and pain can lead to hemodynamic changes involving blood pressure and heart rate (5,6). Such parameters are also affected by certain individual factors such as age, gender, previous experience with dental treatments, and individual psychological response (5).

Anxiety in children undergoing dental treatment is characterized by subjective feelings of tension, apprehension, nervousness, and worry that may be expressed in various forms (7). Severe hemodynamic fluctuations during dental treatment can trigger highly undesirable physical reactions (8), and up to 60% of all children undergoing dental treatment are likely to present negative behavioral changes (7). When this situation is combined with local anesthetics and vasoconstrictors, the undesirable effects upon the cardiovascular system, with the secretion of endogenous catecholamines, may be incremented (9). Thus, the safe and effective treatment of uncooperative children remains a major challenge for dentists (7), and patients under three years of age or with special needs require additional support beyond local anesthesia (4,10).

The term sedation describes a depressed level of consciousness, which varies from light (conscious sedation) to deep sedation, accompanied by increasing depression of the physiological systems (11).

While conscious and moderate sedation is often sufficient for performing the majority of dental treatments in adults, deeper sedation levels or general anesthesia (GA) may occasionally be required in children under 7 years of age and in patients with mental disorders (4, 12-14).

Indications for the use of GA can be classified into three main groups: patients with general medical problems; patients with extensive dental treatment needs;

and patients who do not collaborate at all (13). In children with special needs, there may be criteria justifying more frequent use of GA for dental treatment (13). Recent evidence indicates that parental satisfaction with dental treatment under GA has been continuously increasing over the years and is now accepted more favorably than other active or passive behavioral management techniques (15).

In accordance with the American Academy of Pediatric Dentistry and the American Society of Anesthesiologists (ASA), the anesthesiologist must monitor patients under deep sedation and GA continuously. It is mandatory to monitor oxygenation through pulsioximetry, ventilation through the end-tidal carbon dioxide concentration using capnography and respiratory rate (RR), and hemodynamics through heart rate (HR) and blood pressure (BP) (1,5,9,12,16-19).

Apart from basic monitoring, the bispectral index (BIS) is a tool that is reliable and easy to use for assessment of the depth of sedation or the performance of GA in the clinical setting (20). The bispectral index is a neurophysiological monitoring parameter that has gained popularity in anesthetic practice in recent years (21) (Figure 1). Bispectral index monitoring is a noninvasive technique used in clinical practice to evaluate the level of hypnosis (4,16,20), and was the first technology to be approved by the United States Food and Drug Administration (FDA) in 1996 (16,22,23) to aid in assessing the depth of anesthesia in adults (16,22). This index is based on the principle that the electroencephalographic (EEG) waveforms change with the level of alertness of the patient (16).

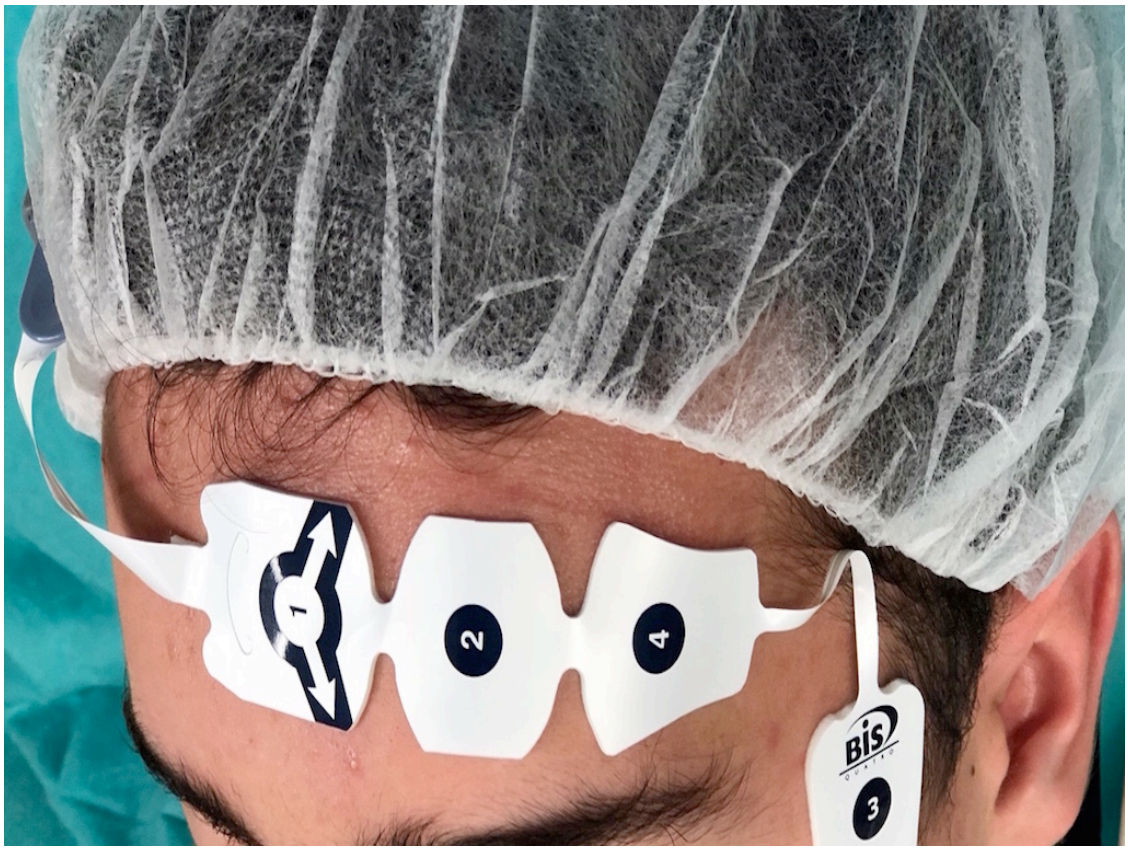

Figure 1. Clinical photograph of BIS electrodes placed on the patient forehead.

The BIS is a dimensionless scale from 100 to 0, where 100 represents an awake clinical state and 0 represents total electrical silence (complete cortical suppression) (22) (Table 1).

90-100	Awake
71-90	Light to moderate sedation
61-70	Deep sedation
40-60	General anesthesia
<40	Deep hypnotic state
0	No brain activity (coma / death)

Table 1. The BIS index.

The usefulness of BIS monitoring during GA has been widely validated in multiple adult and pediatric studies (2,16-18,20,24-26). However, few studies have focused on the particularities of dental treatment in patients with mental disorders.

3. Objectives

Main objective:

To assess the hemodynamic, ventilatory and/or BIS changes that occur in pediatric patients during general anesthesia, intravenous sedation and local anesthesia.

Objectives of the papers:

Paper I

The aim of this systematic review was to evaluate the use of BIS monitoring during intravenous sedation in patients undergoing dental treatment, comparing BIS with sedation scales.

Paper II

The aim of this paper was to compare the observed changes in heart rate, oxygen saturation, respiratory rate, end-tidal carbon dioxide and blood pressure after the administration of propofol and sevoflurane in children with special needs versus healthy children during dental treatment, with the use of BIS monitoring.

Paper III

The aim of this paper was to determine whether the administration of propofol and sevoflurane in general anesthesia contributes to hemodynamic stabilization during dental treatment in healthy children versus the use of local anesthesia alone.

4. Materials and Methods

Paper I

Patient, Intervention, Comparison, Outcome Studies (PICO(S)) Question

This systematic review fulfilled the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-analyses), and PICO(S) questions were applied as assessment criteria to identify the Patient or Population, Intervention, Control and Comparison, Outcome, and Study types (27,28):

P: patients undergoing dental treatment.

I: dental treatment performed under intravenous sedation monitored by BIS.

C: evaluation of patient sedation level using BIS monitoring in comparison with subjective assessment scales.

O: the primary results were the BIS values registered during dental treatment under intravenous sedation; secondary results were the relationship between BIS values and the values obtained from subjective sedation assessment scales.

S: prospective or retrospective clinical studies.

Eligibility criteria

Articles were included in this systematic review if they met the following criteria: 1) clinical studies in humans; 2) a sample size of at least 10 patients; 3) patients older than 3 years and younger than 65 years; 4) randomized and non-randomized prospective studies, cohort studies and retrospective studies; 5) studies of oral/dental treatments performed under intravenous sedation. The exclusion criteria were: 1) studies written in languages other than English; 2) review articles, letters, editorials, doctoral theses or abstracts; 3) studies involving treatments performed under GA and / or inhalation sedation; 4) studies in which the intervention performed was not focused on the oral cavity.

Information sources and search strategy

Electronic and manual literature searches, conducted by two independent reviewers (S.P. and N.L.), covered studies published up until April 2017 across the National Library of Medicine, MEDLINE by PubMed and the Cochrane Library, using different combinations (and the Boolean Operators: AND and OR) of the following search terms / MeSH / key words: “bispectral monitoring” [MeSH term] OR “bispectral analysis” [MeSH term] OR “bispectral index” [MeSH term] AND “dental” [MeSH term] OR “dental treatment” [MeSH term] OR “oral surgery” [MeSH term] OR “implants” [MeSH term]. The screening process consisted of three steps: firstly, by title; secondly, by reading the abstract; and thirdly, by reading the full text article. The information extracted from each of the articles analyzed was entered in a Microsoft Office® Excel spreadsheet (Microsoft Corporation, Redmond, USA). Studies were excluded independently by screening the titles and abstracts by two investigators (S.P. and N.L.), and the final eligibility of an article was confirmed after discussion. In the case of disagreement, and additional investigator (J.G.) was consulted for reaching an agreement. The definitive stage of screening involved full-text reading using the predetermined data extraction form to confirm the eligibility of each study based on the previously mentioned inclusion and exclusion criteria.

Data extraction

The information extracted from each article included: 1) author, year of publication and study type; 2) methods (comparison); 3) dental treatment; 4) patient sample characteristics (number of patients, women, men, mean age and range, ASA score); 5) drugs used for sedation; 6) variables registered; 7) sedation assessment scales used; 7) complications; and 8) study conclusions.

Paper II

Sample description

The present prospective, non-randomized consecutive clinical trial was approved by the Ethics Committee of the Faculty of Dentistry of the University of Murcia (Murcia, Spain) (Committee registry number 1459-2017).

All uncooperative pediatric patients requiring dental treatment in a private clinic in Cartagena (Spain) were considered eligible during the period between September 2019 and March 2020. The inclusion criteria were: a) patient age 2-16 years; b) ASA score I, II or III; c) need for dental treatment (extractions, restorations, pulp therapy, etc.); and d) impossibility to perform treatment under local anesthesia. The exclusion criteria were: a) patients under 2 years or over 16 years of age; and b) ASA score IV.

The study sample consisted of 40 children, considering prior calculation of a sample size of at least 17 individuals per group (with 95% confidence level and an accuracy of ± 5%). The patients were allocated to two groups: 1) a control group of healthy children; and 2) a study group of children with special needs according to the classification of Maeda et al. (23) regarding function, disability and health in relation to the tolerability of dental treatment.

Informed consent was obtained prior to the investigation from all parents after fully explaining the benefits, inconveniences and potential risks of the intervention.

Treatment management

The patients received no anxiolytic premedication before the treatment day. At baseline and prior to the administration of any other drugs, we started continuous monitoring of vital signs with a Datex-Ohmeda Type F-FM Monitor (Instrumentarium Corp., Helsinki, Finland). A pediatric blood pressure cuff was

placed on the right arm; a pulsioximetry probe was attached to the index finger of the left hand; and three electrodes were placed for continuous ECG monitoring. In all cases, BIS monitoring was performed using the Covidien BIS Complete Monitoring System® (Covidien Inc., Mansfield, MA, USA), employing commercially available pediatric BIS sensor strips. Using an algorithm for digital signal processing, a numerical value known as the BIS index was obtained, ranging from 0 to 100, where 0 represents no brain activity (seen in coma and brain death) and 100 indicates an awake patient (4,16, 20) (Table 1). The skin was cleaned with ethanol before the BIS sensor was placed, pressing lightly on the skin for 5 seconds to ensure adhesive contact between the skin and the sensor to ensure good signal quality. The pediatric sensor was placed on the patient forehead and temporal region above the zygomatic arch using self-adhesive. All the monitored parameters were continuously displayed and recorded during the entire dental treatment procedure.

Then, 2% sevoflurane in oxygen was administered on a continuous basis (Mapleson ventilation system, 100% oxygen, 5 l/min). When the BIS values were between 60-70, a venous access was prepared on the back of the right hand using a 22G catheter, with the start of continuous propofol infusion (Target-Controlled Infusion, TCI®; Alaris PK Care Fusion, UK) to obtain a targeting effect compartment concentration of 2 μg/ml in two minutes. At the same time, we started to decrease the inhaled sevoflurane concentration to 1%.

A flexometallic laryngeal mask (LMA, Proseal® airway, Teleflex Medical Europe, Ltd.) (especially designed to isolate the airway from the digestive tract and prevent pulmonary aspiration) of the required number according to the weight of the patient was inserted and fixed on the side opposite to the mouth-opener for continuous oxygen administration (2 l/min), under spontaneous breathing conditions at all times.

Once the anesthetist indicated that optimum sedation had been achieved and was maintained with propofol 2 μg/ml and 1-2% sevoflurane, with the BIS value between 40-60, the dentist began the administration of LA (2% lidocaine with 1:80,000 adrenaline). The amount of LA used was recorded. The patients

remained in a nearly supine position during the dental procedure. Data were recorded at baseline, the start of treatment, and every 15 minutes until the end of the procedure.

Dental treatments were performed using the usual techniques and were recorded for each patient. In those cases where treatment was expected to last long, dexamethasone 0.2-1 mg was administered as an antiinflammatory and antiemetic measure. Atropine 0.01 mg/kg was also administered in order to avoid excess mucous secretion, if required.

In the event of patient discomfort caused by the treatment stimulus (evidenced by movement, complaint, increased HR and/or BP or increased level of consciousness), the anesthetist raised the sevoflurane concentration to 3% for 1-2 minutes and incremented propofol to 2.5-3 μg/ml. We also recorded any unexpected events, such as a need for ventilatory support. In such situations the anesthetist first checked the position of the LMA and set the mandible in hyperextension in order to prevent tube bending and thus facilitate oxygen entry to the airway.

At the end of the dental treatment, propofol and sevoflurane were stopped. When the patient presented a BIS value of 80-90, the LMA was removed and spontaneous breathing was maintained with manual help according to the individual wake-up time. Then, the patient was moved to the anesthesia recovery room with the parents. All patients were kept under observation for 30-45 minutes after surgery, with pulsioximetry and BP monitoring. They were then discharged in accordance with the usual criteria for ambulatory major anesthesia: stable vital signs, the ability to stand, no bleeding, no nausea and/or vomiting, and no moderate or severe pain.

Postoperative instructions were provided, and analgesic (dexketoprofen) and antiemetic medication (metoclopramide hydrochloride) was prescribed. The parents were called by phone on the same day in the afternoon and again on the following day to assess possible complications.

Statistical analysis

The monitoring data collected during the entire procedure were blinded to the main investigator, and a single investigator assessed the level of alertness and recorded all the data in order to eliminate interobserver variability.

Variables such as gender, age, weight, the need for chronic medication, presurgical medication, dental treatment (restorations, pulpotomies, extractions, sealing, topical application of fluoride, tartrectomy, root treatment or the placement of preformed crowns), intravenous sedation drugs and lidocaine carpules were recorded for each group, with the mean and standard deviation (SD).

To study the variation over time of the variables in both groups, two-factor analysis of variance (ANOVA) and the Pearson correlation coefficient were used, with repeated measures to check the effects of time and group, and the interactions between them. A 95% confidence level was considered, with statistical significance being accepted for $p < 0.05$. The Statistical Package for the Social Sciences version 25.0 (SPSS® Inc., Chicago, IL, USA) for MS Windows was used throughout.

Paper III

The present prospective, non-randomized clinical study was approved by the Ethics Committee of the Faculty of Dentistry of the University of Murcia (Murcia, Spain) (Ref.: 1459-2017). Informed consent was obtained from the parents prior to the start of the investigation, explaining to them the procedures, possible discomforts, and risks and benefits involved.

Subjects

The preliminary sample size calculation (with 95% confidence interval [95%CI]) yielded a random sample of 17 individuals per group. Therefore, considering possible dropouts, a total of 40 patients were enrolled in the study (20 per group), selected from two private hospitals during a one-year period (from September 2019 to September 2020), according to the inclusion and exclusion criteria. The inclusion criteria were: a) patients between 2-16 years of age; b) ASA score I (a normal healthy patient) (29); c) patients without associated neurodivergent conditions; d) need for dental treatment (surgical, restorative or root canal treatments); e) dental procedures lasting over 20 minutes (counting from LA infiltration) and less than two hours; and f) the administration of 1-4 carpules of 2% lidocaine with 1:80,000 adrenaline as local anesthesia. The exclusion criteria were: a) ASA score II (a patient with mild systemic disease) (29), III (a patient with severe systemic disease) (29) or IV (a patient with severe systemic disease representing a constant threat to life) (29); b) patients with associated neurodivergent conditions; d) need for sedation (oral or intravenous); c) dental procedures lasting less than 20 minutes or longer than two hours; and d) the administration of less than one or more than four carpules of LA.

The study sample was divided into two groups: 1) general anesthesia group (study group [SG]), involving 20 patients undergoing dental treatment under general anesthesia with local anesthesia infiltration (this group was previously included in another investigation as a control group) (30); and 2) local

anesthesia group (control group [CG]), involving 20 patients undergoing dental treatment with LA infiltration alone.

Patients with needs of dental treatment were recruited and distributed into the study groups according to the described inclusion criteria and, secondly, to the requirement of GA.

All the patients who visited the pediatric dentist at the center were included. All these patients could potentially be referred for GA for dental treatment, and for this reason two years of age was set as the lower limit, since very exceptionally does the specialist visit younger patients. Although they might seem pre-cooperative, those patients were children lacking cooperative ability who were not allowed to undergo treatment using the different management techniques. They suffered severe anxiety, and dental procedures could not be started despite the psychological approaches used. Additionally, some patients had undergone previous attempts of treatment in a conventional setting that had proven unsuccessful. Generally, they made a first visit, as a first contact with the patient (a measure of attempting acclimatization and introducing them to the sights, sounds and smells of the dental environment), and the treatment was attempted in the second appointment. In the event that it could not be carried out with the different behavior modification techniques (two attempts were made, in two different appointments), they were referred to GA after the third visit, with a waiting time of 2-3 weeks.

General anesthesia was performed by a single anesthesiologist and the corresponding dental treatment was performed by a single pediatric dentist.

Study group management

The patients received no anxiolytic premedication the day before surgery. There was a single anesthesiologist for all the treatments. Prior to the administration of any other drugs, baseline vital signs were continuously monitored and recorded (Datex-Ohmeda type F-FM Monitor; Instrumentarium Corp., Helsinki, Finland)

by the anesthesiologist. A pediatric blood pressure cuff was placed on the right arm; a pulsioximetry probe was attached to the index finger of the left hand for the monitoring of SaO_2, and three electrodes were placed for continuous ECG recording. In all cases, BIS monitoring was performed using the Covidien BIS Complete Monitoring System® (Covidien Inc., Mansfield, MA, USA), employing commercially available pediatric BIS sensor strips. The pediatric sensor was placed on the patient forehead and temporal region above the zygomatic arch using self-adhesive. Then, all the monitored parameters were continuously displayed and recorded during the entire dental treatment procedure.

Two percent sevoflurane in oxygen was administered by the anesthesiologist on a continuous basis (Mapleson ventilation system, 100% oxygen, 5 l/min). When the BIS values were between 60-70, a venous access was prepared on the back of the right hand using a 22G catheter, with the start of continuous propofol infusion (TCI®; Alaris PK Care Fusion, UK), to obtain a targeting effect compartment concentration of 2 µg/ml in two minutes. At the same time, we started to decrease the inhaled sevoflurane concentration to 1%.

A Proseal® airway LMA (Teleflex Medical Europe, Ltd.) especially designed to isolate the airway from the digestive tract and prevent pulmonary aspiration, of the required number according to the weight of the patient, was inserted and fixed on the side opposite to the mouth-opener for continuous oxygen administration (2 l/min), under spontaneous breathing conditions at all times.

In those cases where treatment was expected to last long, dexamethasone 0.2-1 mg was administered as an antiinflammatory and antiemetic measure.

Once the anesthesiologist indicated that the optimum hypnotic state had been achieved and was maintained with propofol 2 µg/ml and 1-2% sevoflurane, with a BIS value between 40-60, the dentist began the administration of LA (2% lidocaine with 1:80,000 adrenaline in 1.8 ml carpules). The anesthetic method used involved infiltrative or alveolar nerve block depending on whether the treatment was performed in the maxilla or mandible. The amount of local anesthetic used was recorded. The maximum dose of LA for each patient,

calculated from their weight upon admission, was not exceeded. The treatment was carried out by a single pediatric dentist with more than 15 years of experience in treating children.

In the event of patient discomfort caused by the treatment stimulus (evidenced by movement, complaint, increased HR and/or BP or increased level of consciousness), the anesthesiologist raised the sevoflurane concentration to 3% for 1-2 minutes, and incremented propofol to 2.5-3 μg/ml. We also recorded unexpected events, such as the need for ventilatory support, arrhythmias, vomiting, a dislodged or obstructed endotracheal tube, disconnection of the intravenous line, edema of the tongue or lips, and nasal bleeding as intraoperative complications.

At the end of dental treatment, propofol and sevoflurane were stopped. When the patient presented a BIS of 80-90, the laryngeal mask was removed and spontaneous breathing was maintained with manual help according to the individual wake-up time. Then the patients were moved to the anesthesia recovery room with their parents. All patients were kept under observation for 30-45 minutes after surgery, with pulsioximetry and BP monitoring. They were then discharged in accordance with the usual criteria for major ambulatory anesthesia: stable vital signs, the ability to stand, no bleeding, nausea and/or vomiting, and no moderate or severe pain.

Postoperative instructions were provided, and analgesic (dexketoprofen) and antiemetic (metoclopramide hydrochloride) medication was prescribed. Parents were phone called on the same day in the afternoon and on the following day to assess possible complications.

Control group management

After seating the patient in the dental chair, a blood pressure cuff was wrapped around the right arm and a pulsioximetry probe was attached to the index finger of the left hand. The same monitor (Datex-Ohmeda type F-FM Monitor,

Instrumentarium Corp., Helsinki, Finland) was used to continuously assess the hemodynamic parameters during the entire dental treatment procedure. Then the dentist began the administration of LA (2% lidocaine with 1:80,000 adrenaline in 1.8 ml carpules) not exceeding the maximum dose, based on patient weight. An infiltrative or alveolar nerve block technique was used depending on whether the treatment was performed in the maxilla or mandible, and the amount of local anesthetic used was recorded. The same pediatric dentist carried out the treatment and the same anesthesiologist as in the SG also carried out monitoring and data collection. He was not involved in the data analysis of the study.

After treatment, instructions to be followed by the patient were explained and, if needed, ibuprofen 400 mg every 8 hours was prescribed as analgesia.

Data collection

All the data collected were blinded to the investigator in charge of evaluating the results. A single investigator assessed the level of alertness and recorded the hemodynamic parameters in order to eliminate interobserver variability.

Heart rate, systolic and diastolic blood pressure, and SaO_2 were recorded at baseline (on seating the patient in the dental chair), at the start of treatment (after LA infiltration), and every 10 minutes until the end of treatment. Final data recording was performed when the dental treatment was completely finished in the CG, and when the patient was in the anesthesia recovery room in the SG. Any unexpected events during the entire treatment time and during the postoperative course in both groups were also recorded.

Statistical analysis

The mean of all measurements over the entire period was defined as the central segment of the intervention period. The Shapiro-Wilks test was used to assess the fit to normal distribution of vital signs within each group.

Nonparametric Brunner-Langer models for longitudinal data were applied to determine whether changes in the different vital signs throughout the intervention were similar in both groups (p-value with Bonferroni correction). An ATS-type ANOVA statistic was calculated to evaluate changes throughout the intervention and differences according to the group. The level of significance used was 5% ($\alpha = 0.05$), with a confidence level of 95%. Power analysis was estimated at 99% and 86% for differences over time and between groups, respectively, considering a large effect size to detect f=0.4. The SPSS version 25.0 statistical package (Chicago, IL, USA) was used throughout.

5. Results

Paper I

Study selection

The initial database search identified a total of 119 articles, of which 28 were considered to fulfill the inclusion criteria after assessing the titles and abstracts (with an agreement level between reviewers of 86.41%; kappa = 0.63), and the full text was therefore read in depth. Twelve articles were excluded after reading the full text, as they did not fulfill the inclusion criteria. The reasons for exclusion were: review articles (17,26,31), one short communication (32), no dental treatment performed (33), and treatments performed under GA or nitrous oxide and/or endovenous sedation (2,20,35). Manual searches and cross-referencing did not identify any further works, and so the final selection included a total of 16 articles (1,4,14,18,21,22,35,36,38-45) (Figure 2).

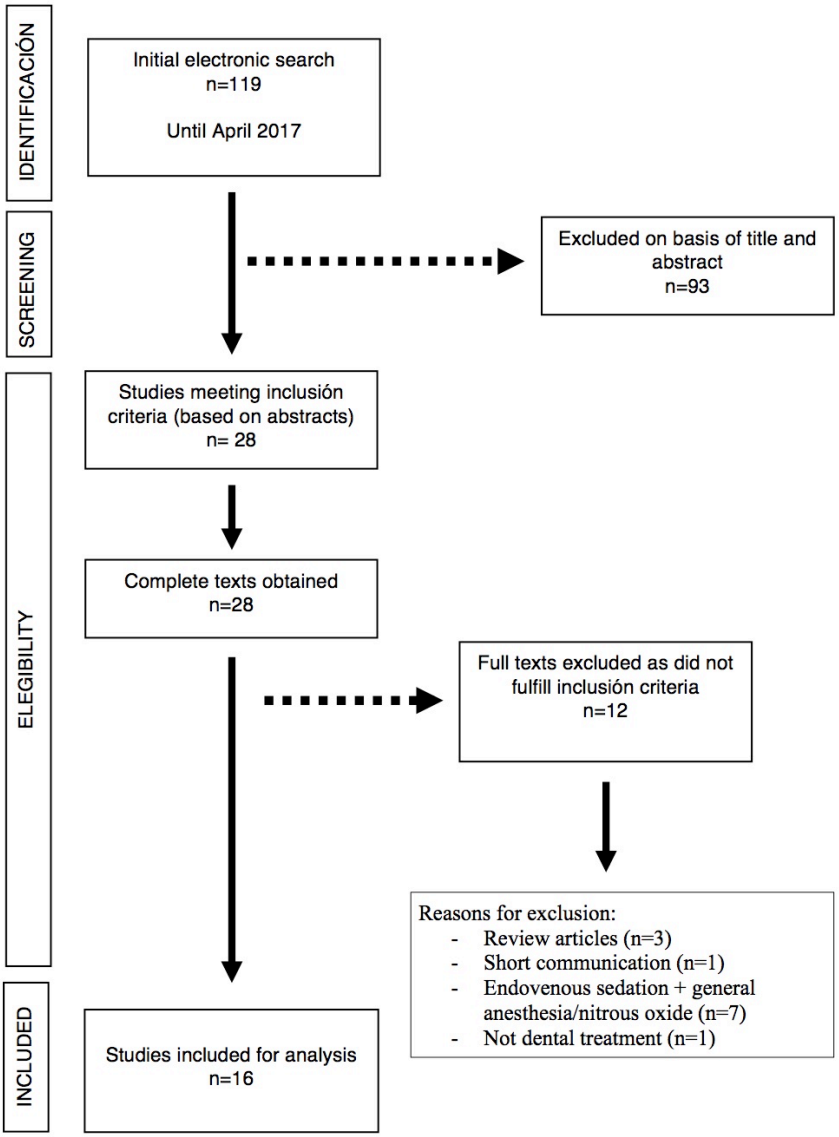

Figure 2. PRISMA flowchart of the selection process.

Characteristics of the analyzed studies

All characteristics of the reviewed articles are shown in Table 2. Of these, two studies involved uncooperative children aged under 8 years (4,38). The rest of the studies involved adults (1,14,18,21,22,35,36,39-45).

	Study 1.Author 2. Year 3. Study type	Methods (comparison)	Dental treatment	Patient sample characteristics 1.Number of patients 2. Women: Men 3. Age (mean years) 4. Age (range, years) 5. ASA score	Sedatives used	Registers	Scales	Complications	Conclusions
	1.Cheung et al 2.2008 3. Prospective cohort study	To evaluate BIS as indicator of level of sedation	3M surgical extraction	1.60 2. 32:28 3. 26.3±6.4/23.8±4.6 4. 18-60 5. I-II	midazolam	HR, BP, RR, OS, BIS	no	2 group A patients OS < 90% and 2 group B patients with dizziness	BIS cannot be used as only indicator of sedation level with i.v. midazolam for 3M surgery but useful to evaluate total dose; helps improve tolerability and safety
	1.Dag et al 2.2014 3. Randomized clinical study	To determine total drug dose and recovery profile of sedated patients comparing BIS with sedation scale	Restorative treatment, extractions	1. 34 2. 14:20 3. 4.74±1.22/ 4.5±0.84 4. 3-6 5. I	midazolam, propofol, remifentanil	HR, OS	UMSS	No	BIS does not offer any advantage over commonly accepted methods of sedation assessment or for determining
	1.Eshghi et al 2. 2017 3. Double-blind randomized clinical study	Compare propofol + midazolam + ketamine vs propofol+ midazolam + remifentanil	Restorative treatment, extractions	1.32 2.15:17 3.4.36±1.6 4.3-7 5. I	midazolam, propofol ketamine or remifentanil	HR, BP, RR, OS, BIS	DSTG	Several patients with nausea and vomiting (remifentanil group)	Intravenous sedation with a combination midazolam, propofol and remifentanil induces effective and safe sedation with less pain, more amnesia and a shorter recovery
	1. Fan et al 2. 2013 3. Double-blind randomized clinical study	Compare efficacy and safety of midazolam vs dexmedetomidine	3M surgical extraction and implant surgery	1.60 2. 42:18 3. 26±7/29±9 4. - 5. I-II	midazolam or dexmedetomidine	HR, BP, RR, OS, BIS	OAA/S	No	Dexmedetomidine is as easy to use as midazolam in dental procedures in outpatient settings and can be used as an alternative to midazolam
	1.Hanamoto et al 2. 2013 3. Prospective cohort study	Evaluate incidence of coughing during implant surgery	Implants	1.147 2. 45:102 3. 59 4. 51.5-65 5. I-II	midazolam, Propofol	HR, BP, OS, BIS	RS	-	Difficulties swallowing and in intraoral fluid suction have varying effects in different surgical areas. Careful water suction must be performed and requires an adequate level of sedation, especially in treating anterior maxillary areas
	1.Ishii et al 2. 2011 3. Prospective cohort study	Evaluate the influence of valproate in total dose of propofol during	Not specified	1.45 2. 25:20 3. 26.5/34 4. 16-38/17-49 5. -	midazolam, TCI propofol	BIS	No	No	Oral valproate reduces the dose of propofol required for sedation; normal doses of propofol

		sedation							can be excessive for patients receiving treatment with oral valproate and may induce complications or delayed recovery from anesthesia
7	1.Maeda et al 2. 2016 3. Retrospective study	Identify factors affecting doses of propofol for sedation	Implants	1.125 2.36:89 3. - 4.56.4 5. I-II	midazolam, TCI propofol	BP, OS	OAA/S	-	The dose of propofol needed to induce adequate moderate sedation is larger for women than men
8	1.Manani et al 2. 2011 3. Randomized clinical study	Compare BIS values with 1 mg diazepam vs 1mg midazolam vs 3mg midazolam	Implants and sinus lift	1. 36 2. 23:13 3. 50.2±12.3/ 45.4±13.9/49.6±8.0 4. - 5. I-II	midazolam or diazepam	BP, OS, BIS, ECG	Rodrigo y Chow clinical sedation assessment scale (1996)	-	In minimum and/or moderate sedation, BIS values and clinical conditions show a safer profile for diazepam than for midazolam
9	1. Mishra et al 2. 2017 3. Randomized clinical study	Compare clinical efficacy of midazolam vs. dexmedetomidine	Oral and maxillofacial surgery	1.60 2. 46:14 3. 33.1±10.4/ 33.97±11.5 4. 18-65 5. I-II	midazolam, or dexmedetomidine	HR, BP, RR, OS, BIS	RS	2 cases of bradycardia, (group D), 2 cases of dizziness (group M), 2 patients with agitation (group not specified)	Dexmedetomidine is an alternative to midazolam for i.v. sedation for oral and maxillofacial surgery under local anesthesia. It is the preferred sedative when a low heart rate, BP, or less amnesia are required. It would appear to be reliable and safe providing sedation without serious secondary effects
10	1.Morse et al 2. 2001 3. Prospective cohort study	Compare BIS with midazolam vs midazolam + ketamine	Oral surgery	1.22 2. 9:13 3. 40±12.8 4. - 5. I	midazolam or midazolam, ketamine	HR, BP, RR, OS, BIS	OAA/S	-	BIS does not provide any additional benefit to the usual methods for monitoring levels of consciousness during sedation for oral surgery
11	1.Muñoz-García et al 2. 2012 3. Randomized clinical study	Evaluate BIS as indicator of level of sedation	Implants, bone regeneration techniques, and connective tissue grafts	1.43 2. 21:22 3. 49.9±0.6/ 55.3±14.3 4. 28-79 5. I-II	midazolam, propofol and fentanyl	HR, BP, OS, BIS	RS	1 patient SO2= 85%	The optimal BIS value during i.v. sedation in outpatient dental treatment appears to be in the range of 80-85, which corresponds to a value of 3 on the Ramsay scale. Consumption of propofol, midazolam and fentanyl are reduced by 30%. The regular use of BIS during sedation improves the efficiency and

									safety of anesthesia
2	1.Sakaguchi et al 2.2011 3. Randomized clinical study	Validate use of BIS with TCI to assess depth of sedation and determine drug dose	Not specified	1.40 2.27:13 3. 30.5±10.8/ 30.5±11.2 4. - 5.I-II	midazolam, propofol	BP, OS, BIS, ECG, EMG (group B)	Assessment of Behavior Reactions Scale	-	The use of BIS together with propofol TCI reduces the propofol dose required and produces faster recovery from sedation
3	1.Sandler et al 2. 2001 3. Randomized clinical study	Evaluate use of BIS compared with OAA/S as indicator of sedation	3M extraction	1.40 2. 23:17 3.22 4.19-33 5. I-II	midazolam, propofol, fentanyl	BP, OS, RR, ECG	OAA/S	2 patients with bradycardia, 1 patient with drowsiness	BIS monitoring is a useful tool for assigning an objective value to the depth of sedation for research purposes and helps induce the required level of sedation using smaller quantities of drugs.
4	1.Sandler and Sparks 2.2000 3. Prospective cohort study	Evaluate usefulness of BIS for determining sedation level in 3rd M extraction	3M extraction	1.25 2. 14:11 3. 25 4. 18-40 5. I-II	midazolam, propofol and fentanyl	BIS	OAA/S	1 patient difficult to sedate laryngospasm	BIS provides an objective measure of the level of sedation. There is a consistent relation between BIS and OAA/S values
5	1.Shah et al 2. 2014 3. Prospective cohort study	Evaluate efficacy of BIS in sedation monitoring with midazolam in dental treatment	Not specified	1.41 2. 42%:58% 3. 40±13.25 4. - 5. I-II	midazolam	HR, BP, OS, BIS	OAA/S	-	BIS can be a useful complementary tool for monitoring the depth of patients undergoing dental treatment using i.v. midazolam but must not be considered as the only sedation monitoring tool
6	1.Taniyama et al 2. 2009 3. Randomized clinical study	Compare dexmedetomidine vs propofol for i.v. sedation	Minor oral surgery	1.14 2. 3:11 3. 31.3±11.8/ 29.4±8.7 4. - 5. I	dexmedetomidine or lidocaine, propofol	HR, BP, OS, BIS,	No	-	There are no statistically significant differences between dexmedetomidine and propofol. Difficult to evaluate sedation levels on the basis of the BIS and so it is necessary to develop better sedation assessment methods

Table 2. Characteristics of the articles included for qualitative synthesis.

All patients corresponded to ASA score I-II (46), with the exception of one investigation that did not provide this information (41,42). Ishii et al. (42) and Sakaguchi et al. (14) conducted studies on adults with intellectual disability.

In 7 studies, the objective was to assess the validity of BIS monitoring in intravenous sedation in patients undergoing dental treatment (1,4,14,21,35,39,45). In the other 7, sedation monitoring was used to compare different sedative drugs (22,36,38,40,42,43,44). In the studies by Maeda et al. (1), Ishii et al. (43) and Hanamoto et al. (41), BIS was used as a further patient monitoring method, along with blood pressure, heart rate, etc.
Fifteen works were prospective studies (4,14,18,21,22,35,36,38-45), and one was a retrospective study (23). Of the prospective studies, 9 were randomized clinical trials (4,14,21,36,38-40,43,44) and 6 were prospective cohort studies (18,22,35,41,42,45). In addition, all were conducted at a single center, most of them in Asia, and more than half in Japan.

Oral / maxillofacial or implant surgeries were the most frequent procedures (21,22,35,36,39-41,43-45), followed by conservative dental treatments or extractions (4,38). Three works did not stipulate the type of dental treatment performed (14,18,42).

Comparisons between sedation scales and BIS values

A strong positive association was observed between the BIS values and other sedation scale scores (Observer's Assessment of Alertness and Sedation Scale, the Ramsay scale, and the University of Michigan Sedation Scale) in four studies (4,18,21,35).

The most widely used scale in the studies reviewed was the OAA/S (18,22,35,39,40), followed by the Ramsay sedation scale (21,41,43). Other

scales used included the UMSS (4), the Assessment of Behavior Reactions Scale (14), Clinical assessment of sedation (36), and the DSTG (38).

The correlation between BIS values and sedation scales has been described in various studies. The BIS value that corresponded to an awake state in the OAA/S (5 points) was 95-99, while medium sedation or relaxation (4 points) corresponded to 75-84, and deep sedation (3 points) corresponded to 70-79 (18). According to Shah, Manley and Craig (18), a BIS range between 75-84 showed a high probability of corresponding to an OAA/S value of 3. According to Sandler and Sparks (35), differentiation between levels of sedation was clear, except for making a distinction between 2 and 3 on the OAA/S. The Ramsay sedation scale and BIS assessment stabilized 5 minutes after commencing sedation and scored 3 on the Ramsay scale and around 85 on the BIS, remaining stable until the intervention had been completed (21). Lastly, Dag et al. (4) also found a clear correlation between mean BIS values and the UMSS, with BIS values between 57-64 corresponding to a UMSS value of 3.

Use of BIS for comparing the different sedatives used in dentistry

Some investigations used the BIS as an objective instrument for measuring sedation and did not question its efficacy or the accuracy of the readings; the authors therefore were confident in using the BIS to compare the efficacy of different drugs for intravenous sedation (36,38,40,43). In this way, they were able to determine which drug is the safest and most effective in groups of patients undergoing specific treatment (36,38,40,43). The BIS scores descended gradually after drug administration and then remained between 80-85, this being indicative of the optimal level of sedation (43,44).

In contrast, BIS analysis during deep sedation of pediatric oral surgery patients did not bring any benefit in comparison with the established methods of conscious sedation assessment according to both Taniyama et al. (44) and Morse et al. (22). Morse et al. (22) did not find BIS to be useful, because the mean BIS values were 90 in their midazolam group and 94 in the midazolam-

ketamine group, and these did not vary much over time with respect to the baseline value - except immediately after inducing sedation, when the values dropped to 85 (22). This would mean that the patient reaches a state of temporary deep sedation, but that this would not be produced if the drug was administered as a continuous slow infusion (22).

Results of BIS monitoring

Two articles reported numerical data obtained from BIS monitoring (38,43) used to determine which minimum and maximum values are adequate for patients undergoing dental treatment (Table 3). These were maintained at 63.01 (5 minutes after starting treatment) and 78.65 (maximum value obtained 45 minutes after starting treatment), obtaining an overall mean of 70.64. The minimum BIS value (38.05) was obtained in the ketamine group and the maximum BIS value (92.48) in the dexmedetomidine group, 45 minutes after the start of the procedure.

Changes in BIS values	BIS values Eshghi (2016) REMIFENTANIL group	BIS values Eshghi (2016) KETAMINE group	BIS values Mishra (2017) DEXMEDETOMIDINE group	BIS values Mishra (2017) MIDAZOLAM group	Minimum mean BIS	Maximum mean BIS	Total mean BIS
5 min	68.62±10.24	50.08±8.39	82.67±7.30	81.17±4.56	63.01	78.26	70.64
25min	65.31±6.72	49.82±10.71	83.60±6.83	79.73±7.43	61.69	77.54	69.62
45 min	69.71±4.57	50±11.95	84.33±8.15	82.55±3.33	64.65	78.65	71.65
							70.64

Table 3. BIS numerical data.

Paper II

Sample description

The study sample of 40 patients comprised children between 2 and 13 years of age. The control group consisted of 19 healthy children (9 males and 10 females), and the study group consisted of 21 patients (13 males and 8 females), presenting the following mental disorders: 7 with autism spectrum disorder (one of them also with Asperger's syndrome), 5 with Down syndrome, four with chronic encephalopathy, one with Cayler syndrome, one with Turner syndrome, one with cerebral palsy, one with hydrocephalus and one with language disorder.

The CSN group was significantly older than the HC group (mean 8 ± 2.7 versus 5.5 ± 1.8 years; p=0.001). Nevertheless, the groups were homogeneous in terms of gender, body weight, chronic medication, presurgical medication and drugs administered during the treatment provided in the study (p>0.05). The descriptive and comparative analysis of the drug doses showed that the patients in both groups received similar intravenous agents (propofol, sevoflurane), with no significant differences between them (p<0.05). Likewise, no significant differences were observed in terms of the local anesthesia administered in both groups (p<0.05) (Table 4).

	HC group Mean (SD)	CSN group Mean (SD)	P- value
Gender, n (%) Male Female	 9 (47.4) 10 (52.6)	 13 (61.9) 8 (38.1)	0.356
Age (years)	5.2 (1.8)	8 (2.7)	0.001
Weight (kg)	22.9 (7.2)	30.3 (12.3)	
Chronic medication No Yes	 19 (100)	 15 (71.4) 6 (28.6)	

Presurgical medication, n (%) No Yes	 14 (73.7) 5 (26.3)	 18 (85.7) 3 (14.3)	0.342
Dental restorations, mean (SD)	3.7 (2.4)	3.4 (2.4)	0.645
Pulpotomies, mean (SD)	0.9 (1.7)	0.6 (0.9)	0.453
Extractions, mean (SD)	0.5 (1.1)	1.4 (1.9)	0.087
Sealing, mean (SD)	1.3 (2.3)	1.4 (1.5)	0.788
Topical fluoride, n (%) No Yes	 8 (42.1) 11 (57.9)	 2 (9.5) 19 (90.5)	0.017
Tartrectomy, n (%) No Yes	 13 (68.4) 6 (31.6)	 4 (19) 17 (81)	0.002
Root treatment, n (%) No Yes	 16 (84.2) 3 (15.8)	 19 (90.5) 2 (9.5)	0.55
Placement of preformed crowns, n (%) No Yes	 18 (94.8) 1 (5.3)	 21 (100)	0.287
Intravenous sedation drugs, mean (SD) Propofol Sevoflurane	 277.89 (71.23) 0.28 (0.78)	 321.90 (200.34) 0.49 (1.00)	 0.124 0.456
Lidocaine carpules, mean (SD)	2.18 (1.16)	2.14 (0.73)	0.892

Table 4. Demographic data, patient treatment and intravenous sedation drugs employed.

Dental treatment description

Dental treatments comprised the topical application of fluoride, tartrectomy, restorations, pulp therapies and extractions, with the use of local anesthesia when needed. No statistically significant differences ($p>0.05$) between the two groups were observed in terms of the dental treatments provided, with the

exception of the topical application of fluoride (p=0.017) and tartrectomy (p=0.002). Topical fluoride application was performed in 90.5% of the patients in the CSN group, and in 57.7% of the patients in the HC group. Similarly, tartrectomy was performed in 81% of the patients of the CSN group, versus in 31.6% of the patients in the HC group. All these data are fully described in Table 4.

Hemodynamic and ventilatory parameters

A significant decrease in SBP, DBP and RR was observed over time ($p < 0.001$), though no statistically significant differences were recorded between the two groups for any of these variables.

Heart rate also decreased significantly over time. In both groups, HR decreased significantly at the treatment starting timepoint versus the baseline value, and remained without statistically significant changes from that moment until the end of the study. However, there was also a significant interaction effect between both groups over time. The mean HR from the start of the intervention until the end of treatment was significantly lower in the CSN group (100.67 bpm) than in the HC group (108.09 bpm) ($p = 0.012$) (Figure 3).

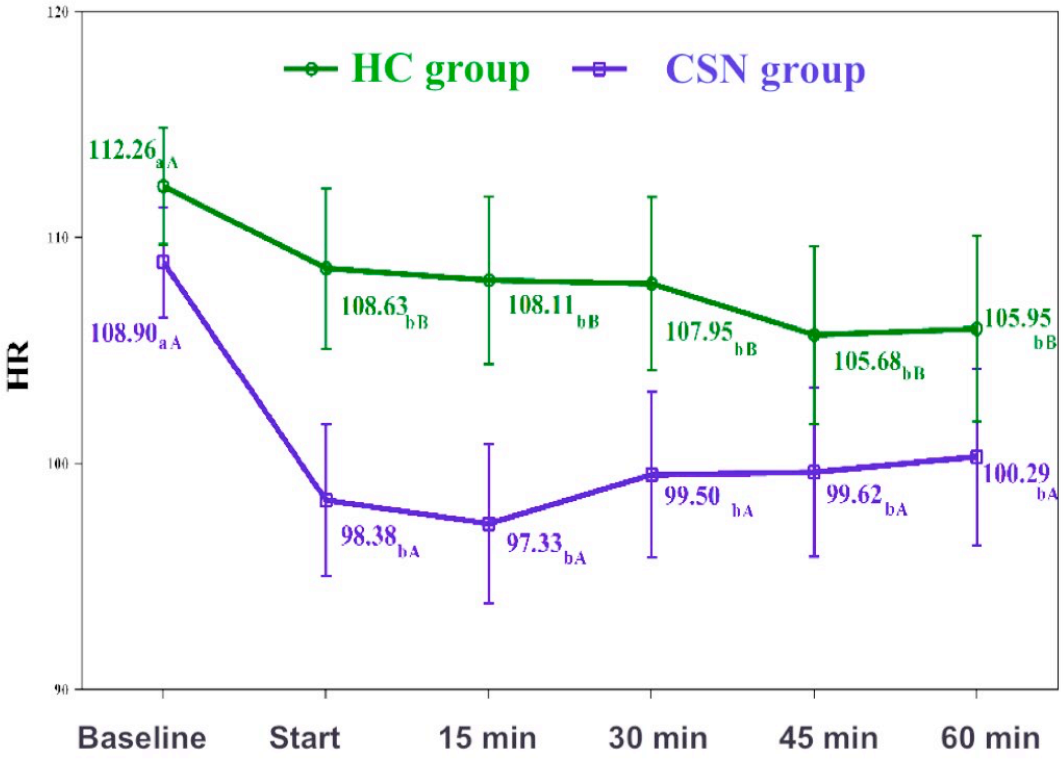

Figure 3. Heart rate. Group and time interaction.
a-d. Two-by-two comparisons. In the same group, different lowercase letters indicate statistically significant differences between the timepoints (Bonferroni correction).
A-B. Two-by-two comparisons. At the same timepoint, different capital letters indicate statistically significant differences between the groups (Bonferroni correction).

Lastly, in relation to the variables SaO_2 and exhaled CO_2, no statistically significant differences were observed over time and no interactions between the two groups were recorded.

Bispectral monitoring

The BIS values also decreased significantly over time in both groups. Likewise, there was a significant interaction effect between the two groups. In this case, there was a statistically significant decrease from the start of treatment until the 30-minute timepoint. From this moment until the end of the study, there were no statistically significant changes in either of the two groups. However, from the start of the intervention, the BIS values in the CSN group were significantly lower than in the HC group ($p = 0.043$) (Figure 4, Table 5). The mean BIS value

in the CSN group was 55.77 versus 63.06 in the HC group. The lowest mean BIS value was 43.95, and was recorded at minute 45 in the CSN group.

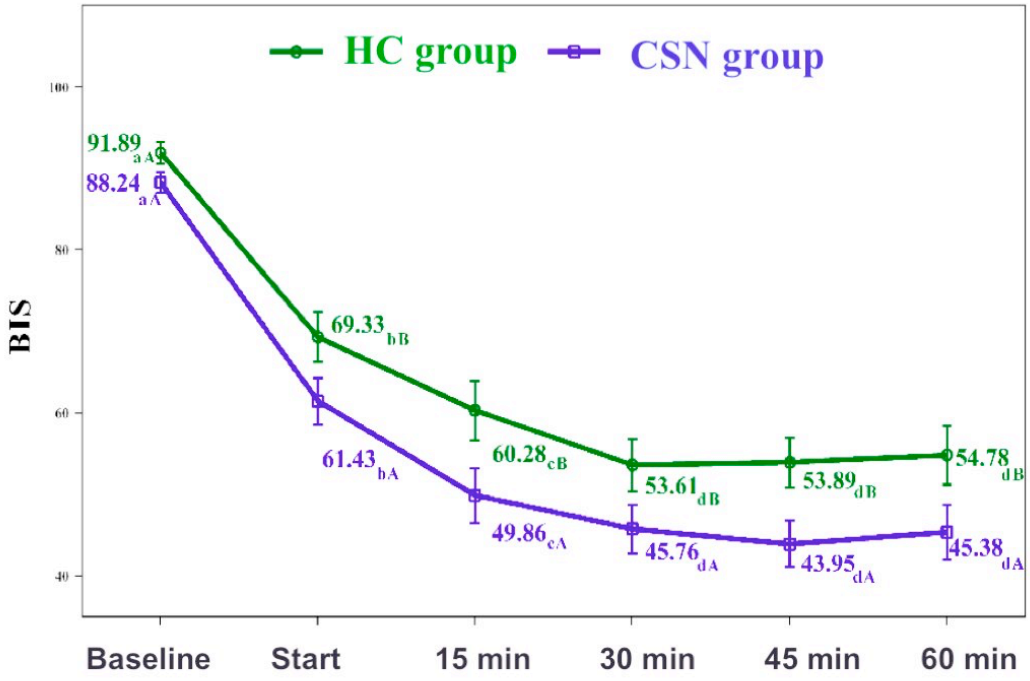

Figure 4. BIS value. Group and time interaction.
a-d. Two-by-two comparisons. In the same group, different lowercase letters indicate statistically significant differences between the timepoints (Bonferroni correction).
A-B. Two-by-two comparisons. At the same timepoint, different capital letters indicate statistically significant differences between the groups (Bonferroni correction).

	Measurement, mean (SD)						Intra-subject effects†	
	Baseline	Start	15 min	30 min	45 min	60 min	Time	Group*Time
							P-value	P-value
SBP							P < 0.001 (0.358)	p = 0.187 (0.042)
HC	97.21 (7.19)	93.84 (4.78)	92.74 (7.00)	92.84 (7.85)	91.89 (6.79)	92.63 (5.48)		
CSN	100.29 (7.87)	94.19 (4.95)	92.76 (5.38)	92.14 (5.52)	90.95 (5.87)	92.14 (6.00)		
Total	98.83 (7.62)	94.03 (4.81)	92.75 (6.12)	92.48 (6.65)	91.40 (6.26)	92.38 (5.69)		
DBP							p< 0.001 (0.33)	p = 0.538 (0.016)
HC	60.21 (2.88)	58.74 (3.63)	57.16 (5.25)	55.16 (6.91)	54.79 (8.10)	55.00 (8.60)		
CSN	61.24 (3.70)	58.67 (2.61)	56.67 (4.79)	56.38 (4.66)	55.00 (5.83)	53.95 (5.85)		
Total	60.75 (3.33)	58.70 (3.10)	56.90 (4.96)	55.80 (5.79)	54.90 (6.91)	54.45 (7.21)		
SaO_2							p = 0.259(0.034)	p = 0.286 (0.031)
HC	99.11 (0.58)	98.50 (1.25)	98.89 (0.83)	93.44 (22.09)	98.61 (1.09)	98.83 (0.92)		
CSN	99.05 (1.02)	98.67 (1.28)	98.62 (1.28)	98.52 (1.21)	98.48 (1.03)	98.43 (0.98)		
Total	99.08 (0.84)	98.59 (1.25)	98.74 (1.09)	96.18 (15.02)	98.54 (1.05)	98.62 (0.96)		
HR							p = 0.002(0.136)	p = 0.012 (0.0117)
HC	112.26 (10.35)	108.63 (12.23)	108.11(14.68)	107.95 (15.27)	105.68 (16.75)	105.95 (17.55)		
CSN	108.90 (11.98)	98.38 (17.73)	97.33 (17.33)	99.50 (17.91)	99.62 (17.35)	100.29 (18.26)		
Total	110.58 (11.10)	103.51 (15.22)	102.72(16.04)	103.73 (16.53)	102.65 (16.85)	103.12 (17.70)		
RR							p < 0.001(0.562)	p = 0.576 (0.016)
HC	25.21 (5.99)	22.37 (5.56)	21.42 (5.59)	20.74 (5.00)	20.11 (5.12)	19.16 (5.47)		
CSN	22.95 (6.74)	20.29 (7.42)	19.62 (7.41)	18.62 (5.95)	18.86 (6.58)	17.90 (6.69)		
Total	24.02 (6.42)	21.27 (6.61)	20.47 (6.59)	19.62 (5.56)	19.45 (5.89)	18.50 (6.10)		
Exhaled CO2							p = 0.454(0.018)	p = 0.197 (0.009)
HC	46.72 (5.48)	45.89 (4.30)	44.89 (6.79)	45.00 (6.87)	44.44 (5.73)	43.83 (5.13)		
CSN	39.67 (11.49)	42.52 (7.28)	43.57 (7.08)	45.38 (7.85)	44.90 (7.84)	44.76 (7.52)		
Total	42.92 (9.78)	44.08 (6.25)	44.18 (6.89)	45.21 (7.32)	44.69 (6.86)	44.33 (6.46)		
BIS value							p < 0.001 (0.76)	p = 0.043 (0.097)
HC	91.89 (5.39)	69.33 (11.10)	60.28 (13.25)	53.61 (13.25)	53.89 (12.73)	54.78 (14.63)		
CSN	88.24 (5.94)	61.43 (14.53)	49.86 (17.02)	45.76 (14.00)	43.95 (13.09)	45.38 (15.97)		
Total	90.07 (6.09)	65.38 (13.23)	55.07 (15.78)	49.69 (13.80)	48.92 (13.37)	50.08 (15.62)		

Table 5. Variation of the study variables over time.

The variation over time of the hemodynamic and ventilatory parameters (SBP and DBP, SaO_2, HR, RR, CO_2) and the BIS values between the two groups is summarized in Table 5. No intra- or postoperative complications were recorded.

Paper III

Sample description

Forty patients were initially enrolled in the study between September 2019 and September 2020. One patient was excluded due to data recording issues. The final sample distribution was 19 patients undergoing dental treatment under general and local anesthesia (SG), and 20 controls undergoing dental treatment with local anesthesia only (CG). The gender distribution was 7 males and 12 females in the SG and 15 males and 5 females in the CG. The mean patient age was 5.2±1.8 years in the SG (range 2-8 years) and 10.4 ± 3.3 years in the CG (range 6-16 years). The allocation of patients to each of the groups resulted in a lower age for patients in the GA group versus patients in the LA only group. Thus, since the vital constants could be influenced by the age of the patient, changes in the constants throughout the treatment were assessed to determine whether they were similar in both groups.

All the treatments were performed using the standard techniques, involving restorations, pulp therapies, extractions of temporary and permanent teeth, topical applications of fluoride, ultrasonic scaling, sealants and crowns. In the SG, we performed 71 restorations, 20 pulp therapies, 10 extractions, 24 sealant applications, 11 topical applications of fluoride, 6 ultrasonic scalings and 4 crowns. In the CG the number of restorations was 16, with a single pulp treatment, 7 extractions and two sealant applications. No crowns or ultrasonic scaling were performed in this group (Table 6). Finally, the mean number of local anesthetic carpules used was 0.95 (range 0-1.5) and 2.18 (range 1-4) in the study and control group, respectively.

		GROUP					
		Total		CG		SG	
		N	%	N	%	N	%
RESTORATIONS	Total	39	100.0%	20	100.0%	19	100.0%
	0	10	25.6%	6	30.0%	4	21.1%
	1	12	30.8%	12	60.0%	0	.0%
	2	3	7.7%	2	10.0%	1	5.3%
	3	2	5.1%	0	.0%	2	10.5%
	4	4	10.3%	0	.0%	4	21.1%
	5	4	10.3%	0	.0%	4	21.1%
	6	2	5.1%	0	.0%	2	10.5%
	7	1	2.6%	0	.0%	1	5.3%
	8	1	2.6%	0	.0%	1	5.3%
PULP THERAPIES	Total	39	100.0%	20	100.0%	19	100.0%
	0	30	76.9%	19	95.0%	11	57.9%
	1	6	15.4%	1	5.0%	5	26.3%
	2	1	2.6%	0	.0%	1	5.3%
	3	1	2.6%	0	.0%	1	5.3%
	7	1	2.6%	0	.0%	1	5.3%
EXTRACTIONS	Total	39	100.0%	20	100.0%	19	100.0%
	0	29	74.4%	15	75.0%	14	73.7%
	1	5	12.8%	3	15.0%	2	10.5%
	2	4	10.3%	2	10.0%	2	10.5%
	4	1	2.6%	0	.0%	1	5.3%
TOPICAL FLUOR	Total	39	100.0%	20	100.0%	19	100.0%
	No	27	69.2%	19	95.0%	8	42.1%
	Yes	12	30.8%	1	5.0%	11	57.9%
ULTRASONIC SCALING	Total	39	100.0%	20	100.0%	19	100.0%
	No	33	84.6%	20	100.0%	13	68.4%
	Yes	6	15.4%	0	.0%	6	31.6%
SEALANTS	Total	39	100.0%	20	100.0%	19	100.0%
	0	30	76.9%	18	90.0%	12	63.2%
	1	4	10.3%	2	10.0%	2	10.5%
	2	2	5.1%	0	.0%	2	10.5%
	4	1	2.6%	0	.0%	1	5.3%
	7	2	5.1%	0	.0%	2	10.5%
ROOT TREATMENT	Total	39	100.0%	20	100.0%	19	100.0%
	No	36	92.3%	20	100.0%	16	84.2%
	Yes	3	7.7%	0	.0%	3	15.8%
PREFORMED CROWNS	Total	39	100.0%	20	100.0%	19	100.0%
	0	37	94.9%	20	100.0%	17	89.5%
	1	1	2.6%	0	.0%	1	5.3%
	3	1	2.6%	0	.0%	1	5.3%

Table 6. Dental treatment performed in the patients (CG and SG distribution). (CG: control group, SG: study group).

Systolic blood pressure

Systolic blood pressure showed a statistically significant decrease ($p<0.001$) in SG. In contrast, in CG the SBP values were characterized by a stable pattern ($p=0.106$) (Figure 5). The marked decrease observed in the GA patients was related to the initial dose of propofol administered ($p=0.088$), but not to the dose of sevoflurane: a higher dose of propofol (≥ 200 mg) resulted in a more intense drop in SBP and also a stronger subsequent recovery.

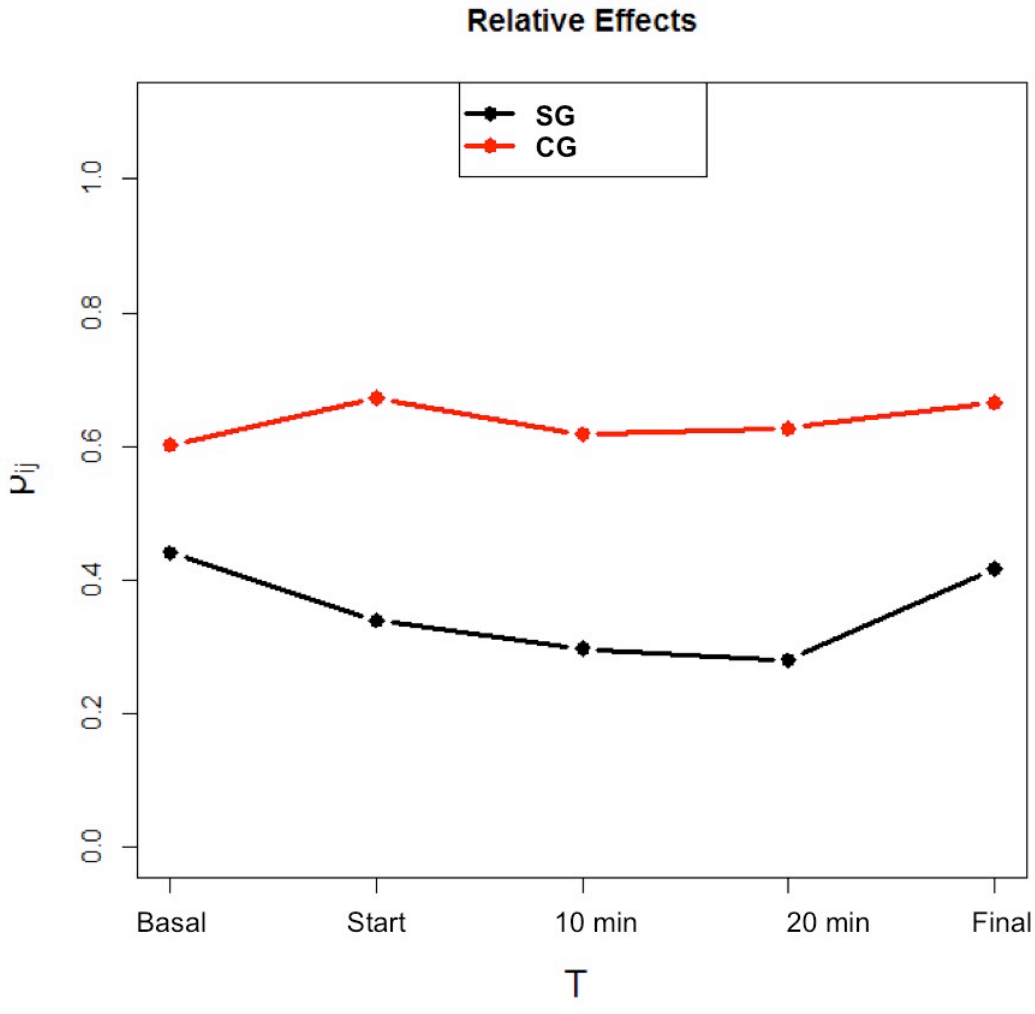

Figure 5. Relative effects of SBP changes over time (SBP: systolic blood pressure; SG: study group - general anesthesia with local anesthesia; CG: control group - local anesthesia alone; P: relative effects; min: minutes; T: time).

The evolution of SBP in the CG was not the same in those under versus over 10 years of age (p=0.033): the SBP value tended to rise (p=0.071) in patients under 10 years of age and proved more stable or even exhibited a downward trend among those ≥ 10 years of age (p=0.197).

The evolution of SBP over time is represented in Figure 6 and Table 7.

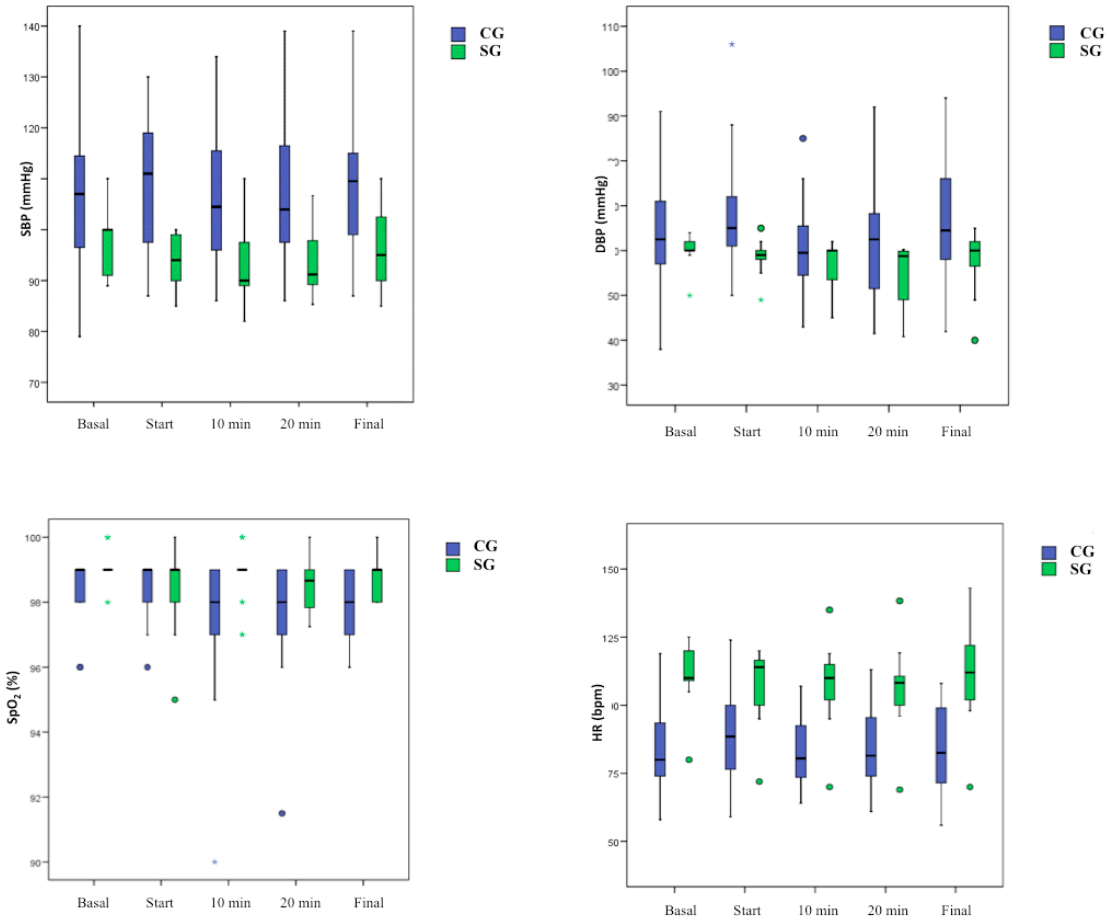

Figure 6. Evolution of the four variables (SBP: systolic blood pressure, DBP: diastolic blood pressure, SaO_2: oxygen saturation; HR: heart rate) over time according to each study group.

		Basal	Start	10 min	20 min	Final	
SBP	**CG**	107.0	111.0	104.5	104	109.5	Time **p=0.033***
	SG	100.0	94.0	90.0	91.2	95.0	Group **p<0.001*****
							Interaction **p=0.035***
DBP	**CG**	62.5	65.0	59.5	62.5	64.5	Time **p=0.033***
	SG	60.0	59.0	60.0	58.8	60.0	Group **p<0.001*****
							Interaction **p=0.035***
SaO_2	**CG**	99.0	99.0	98.0	98.0	98.0	Time p=0.007**
	SG	99.0	99.0	99.0	98.7	99.0	Group p=0.012*
							Interaction p=0.079
HR	**CG**	88.0	88.5	80.5	81.5	82.5	Time p=0.066
	SG	110.0	114.0	110.0	108.3	112.0	Group **p<0.001*****
							Interaction p=0.052

Table 7. Evolution of the four variables (SBP, DBP, SaO_2 and HR) during the intervention by group; median and results of the ATS test of the Brunner-Langer model in relation to time and group (p-value) (SBP: systolic blood pressure, DBP: diastolic blood pressure, SaO_2, HR: heart rate).

Diastolic blood pressure

Diastolic blood pressure behaved in the same way as SBP in the SG, with more stable values in the CG (p=0.106). General anesthesia caused a more sustained decrease and later recovery of DBP throughout the intervention (p<0.001) (Figure 7). The changes in DBP were significantly conditioned by the dose of propofol and sevoflurane administered. A lower propofol dose (150 mg) caused DBP to decrease progressively until final recovery (p=0.045). The same effect was caused by a higher dose of sevoflurane (≥ 2%), where there was a clearer decrease in the parameter (p = 0.039). The DBP values proved more stable in the CG, in line with what was observed with SBP. However, no differences were observed between age levels (p = 0.641).

The evolution of DBP over time is represented in Figure 6 and Table 7.

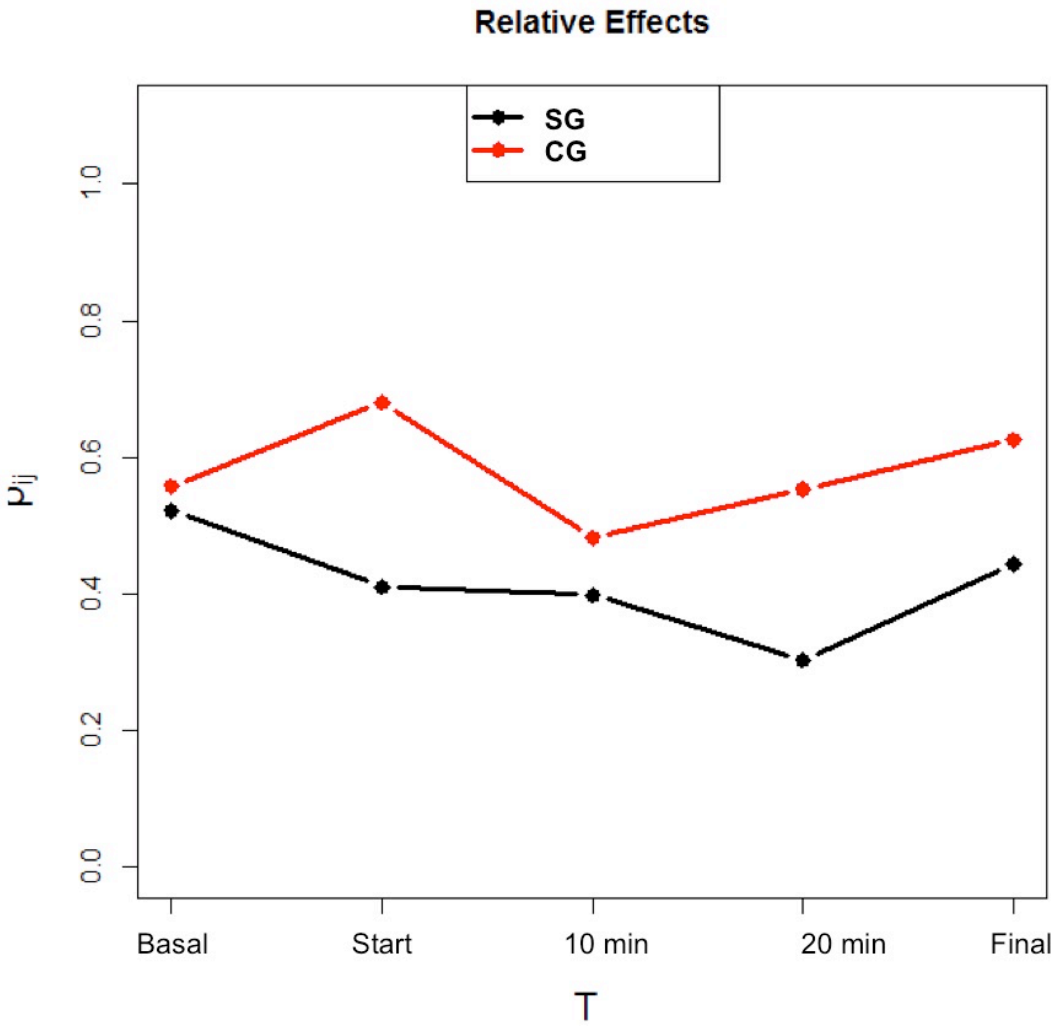

Figure 7. Relative effects of DBP changes over time (DBP: diastolic blood pressure; SG: study group - general anesthesia with local anesthesia; CG: control group - local anesthesia alone; P: relative effects; min: minutes; T: time).

Oxygen saturation

The SaO_2 values decreased significantly throughout treatment in both groups ($p = 0.007$) (Figure 8). The reduction of this parameter was slightly greater at the beginning of treatment in the SG ($p = 0.01$) compared to the CG ($p = 0.068$), though the local anesthesia patients exhibited lower SaO_2 over the treatment period than the GA patients. In the SG, the changes in saturation were significantly related to the dose of propofol administered ($p = 0.002$) - a higher dose ($\geq$ 200 mg) resulting in clearer stabilization of SaO_2.

The evolution of SaO_2 over time is represented in Figure 6 and Table 7.

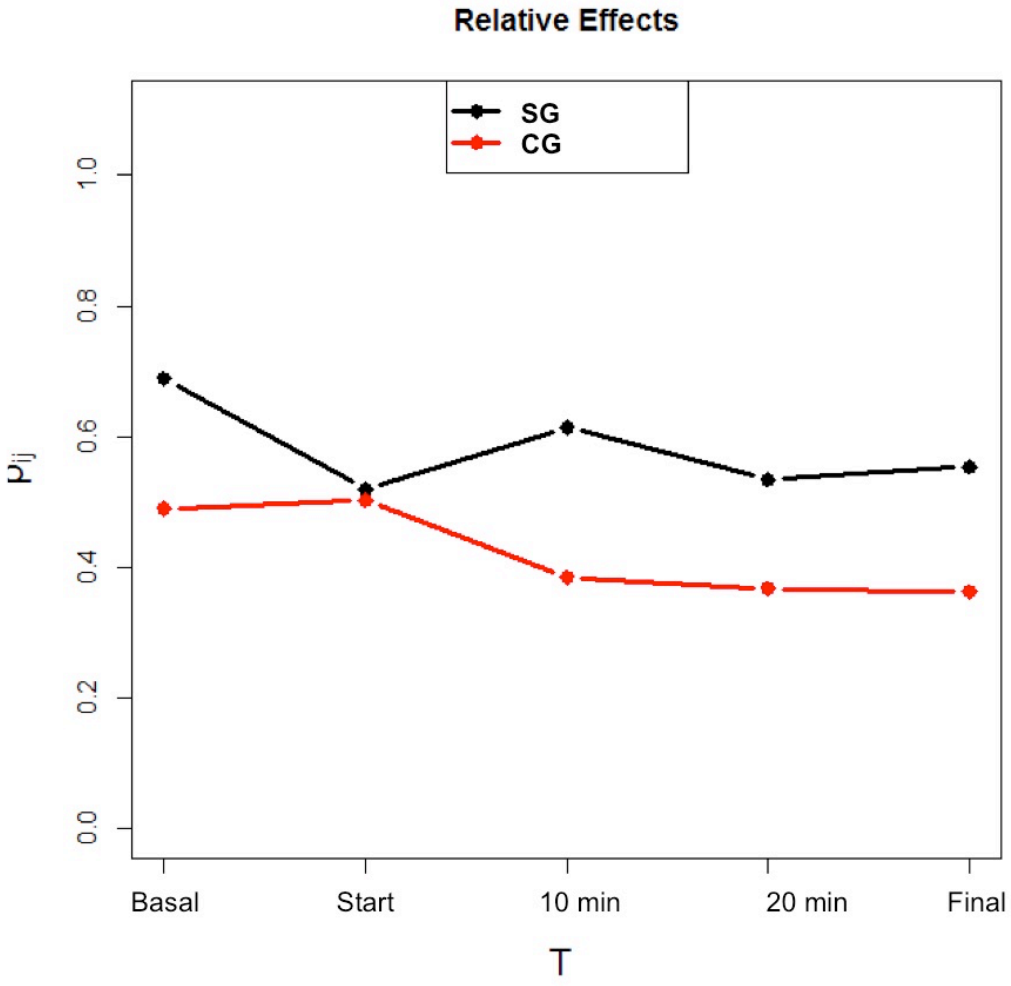

Figure 8. Relative effects of SaO_2 changes over time (SaO_2: oxygen saturation; SG: study group - general anesthesia with local anesthesia; CG: control group - local anesthesia alone; P: relative effects; min: minutes; T: time).

Heart rate

As with the previous parameters, GA caused a clearer decrease in HR, although the mean value was lower in the local anesthesia patients than when using GA, and the time course throughout dental treatment proved different in each group: HR decreased more clearly during treatment in the SG (p=0.021), compared with greater stability in the CG (p=0.263) (Figure 9). In contrast to

SBP and DBP, the changes in HR were not dependent upon the dose of propofol dose administered, but were positively influenced by sevoflurane: a higher dose of sevoflurane (≥ 2%) resulted in a more noticeable drop in HR (p=0.047).

The evolution of HR over time is represented in Figure 6 and Table 7.

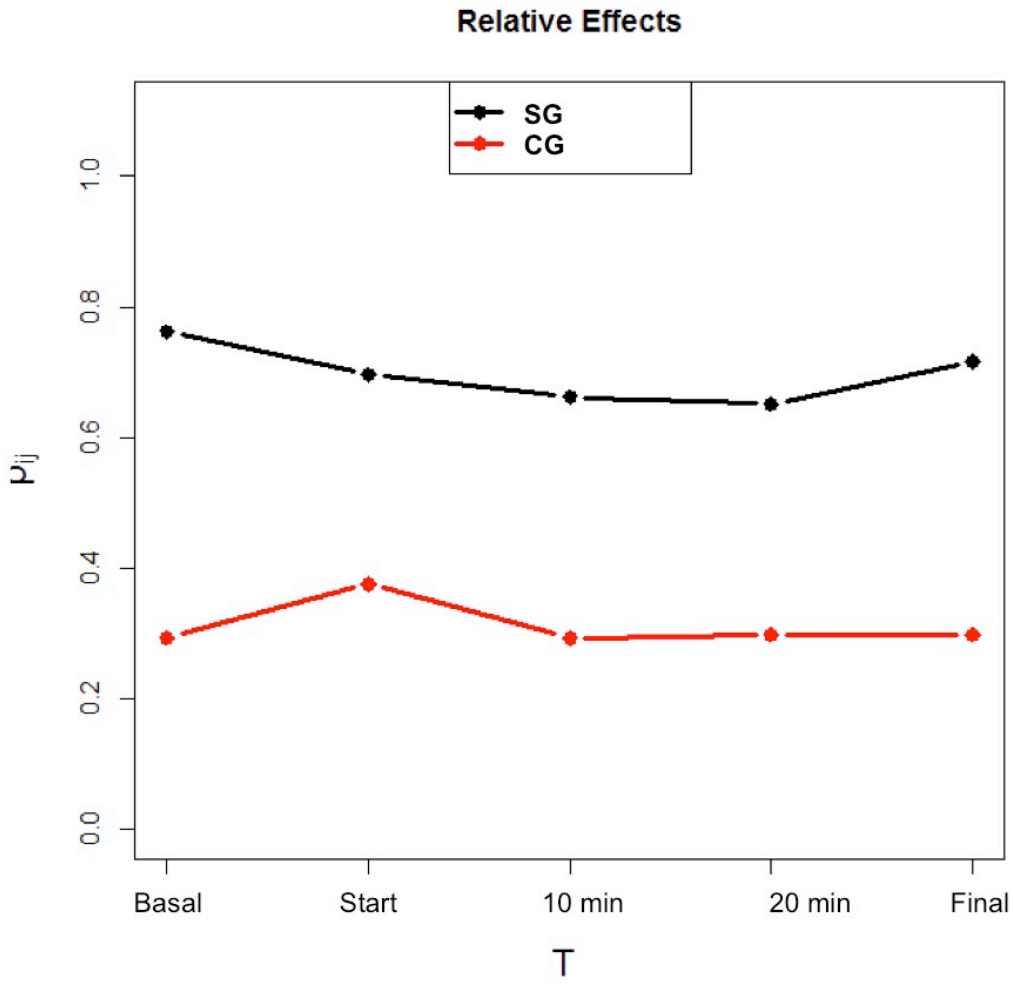

Figure 9. Relative effects of HR over time (HR: heart rate; SG: study group - general anesthesia with local anesthesia; CG: control group - local anesthesia alone; P: relative effects; min: minutes; T: time).

Other analyses

As we have mentioned, SBP remained stable in the CG. However, the evolution was not the same in those younger versus older than 10 years (p=0.033). Among children under 10 years of age, SBP tended to increase (p=0.071), while among those over 10 years of age, more stability or even a downward trend was observed (p=0.197).

In the SG, the SBP values changed significantly over time (p=0.002), but following a similar pattern regardless of patient age (p=0.479).

The evolution of SaO_2 in the SG was conditioned by the age of the patient (p=0.012). In those patients under 5 years of age we recorded a rapid drop in the parameter at the start of the intervention, while in those over that age the drop occurred towards the end of the intervention. In the CG, the decrease occurred in a similar way in both age groups.

Diastolic blood pressure, HR, patient gender and the total dose of local anesthetic used had little influence upon the evolution of the vital constants.

Lastly, no side effects such as nausea, vomiting, respiratory depression or tachycardia were observed in any patients in either group. There was only one case of disconnection of the intravenous line and another in which the endotracheal tube was dislodged. In both cases the anesthesiologist quickly resolved the problem, and dental treatment could continue without further incidents.

6. General discussion

Dental anxiety is a prevalent phenomenon that can complicate the provision of dental treatment under appropriate safety standards in pediatric patients (5,9). An increase in BP and HR can be expected during dental treatment, and this can result in altered cardiac rhythm, angina or myocardial infarction in patients with established cardiovascular disorders - though such complications can also be found in healthy patients (5). Therefore, a good and effective alternative in the case of pediatric patients is to perform dental treatment under intravenous sedation or GA in order to reduce dental anxiety, provide a comfortable and reliable surgical environment (47), and prevent stress-related complications during dental treatment (4).

Most dental procedures can be performed in pediatric patients using non-pharmacological behavioral-based measures, though nitrous oxide inhalation offers good results in children with mild anxiety levels (47). However, the success rate with conscious sedation is low in patients with severe anxiety, and deep sedation with intravenous agents or GA may be a better option for dental treatment in such cases (47).

General anesthesia can assist in providing quality dental care in many patients who could not be treated otherwise. This is especially true for children with special needs who increasingly attend dental clinics for treatment (13). In this regard, the American Academy of Pediatric Dentistry defines children with special health care needs as those who have “any physical, developmental, mental, sensory, behavioral, cognitive or emotional impairment or limiting condition that requires medical management, health care intervention, and/or the use of specialized services or programs“ (48).

On comparing the hemodynamic parameters between healthy children under GA versus LA alone, the prospective study published on Special Care in Dentistry showed a decrease in BP, HR and SaO_2 in GA patients. Nevertheless, SaO_2 proved to be more stable and with values closer to baseline over the treatment period in the GA patients.

Our study showed SBP, DBP and HR to decrease significantly throughout dental treatment in GA patients, and found SaO_2 to be more stable and with better values in patients under GA due to the fact that the continuous airway supply of oxygen is maintained with the laryngeal mask. This is partially in agreement with the findings of Saravia et al. (49) and Patterson et al. (50), who reported fluctuations in SBP during treatment under sedation, but without statistically significant variations between the preoperative and operative readings. Although dental manipulation causes a significant increase in SBP in sedated patients (50), our study evidenced a significant decrease in SBP in the GA group, without changes related to local anesthetic injection or dental manipulation. The absence of changes was probably a consequence of the deep level of anesthesia achieved due to 2% sevoflurane, and the decrease was related to the propofol dose administered - observing a greater drop and greater ultimate recoveries with higher doses of the drug. In line with these observations, Canpolat et al. (47) found mean arterial pressure to always be lower when they administered propofol versus other drugs in pediatric sedation.

Overall, the significant decrease in SBP found in the GA group (SG) contrasted with the more stable pattern observed in the LA group (CG). Although we recorded an increase in SBP after the injection of local anesthetic in the CG, it failed to reach statistical significance. This is in line with the results of Sanadhya et al. (9), who found SBP to be highest during local anesthetic injection, followed by during tooth extraction in non-sedated patients. The increase in SBP after the injection has been related to the combination of the epinephrine concentration contained in the local anesthetic solution (5) and the possible association between emotional stress and fear with sympathetic activity (tachycardia) - with an increase in the plasma concentrations of adrenaline and norepinephrine, or both (9).

In contrast to our findings, Patterson et al. (50) and Sanadhya et al. (9) reported a significant increase in DBP related with the injection of anesthesia and/or dental manipulation in sedated and non-sedated patients. In our study, the significant decrease seen in DBP in the GA group was related to a lower dose

of propofol (150 mg) and to a higher dose of sevoflurane (≥ 2%), and was not related at all to anesthesia injection or dental manipulation. Furthermore, our series confirmed the stability of DBP, with no significant differences among the 5 study timepoints in the local anesthesia patients.

No hypoxia episodes were recorded in our study, but SaO2 was the only variable that failed to recover at the end of treatment with respect to the baseline value in the SG. There was a clear stabilization of SaO2 when a higher propofol dose was administered, and SaO2 was also higher in the SG throughout the entire period than in the CG - reflecting better control of this parameter when using the GA approach.

Regarding heart rate, we observed an increase after the injection of local anesthetic in the CG, though without reaching statistical significance. These findings are in agreement with those of Sanadhya et al. (9), who found HR to be highest during local anesthetic injection, followed by during tooth extraction in non-sedated patients, and this was moreover associated to anxiety. The association between emotional stress and fear with sympathetic activity (50) (tachycardia), with an increase in the plasma concentrations of adrenaline and norepinephrine, or both mechanisms, could explain these effects (9). In addition, the significant decrease in HR in the SG recorded in our study did not depend on the dose of propofol administered but was influenced by the dose of sevoflurane - higher doses of the latter drug resulting in a greater decrease in HR. In contrast, some studies have found that other sedative drugs such as ketamine induce a statistically significant increase in HR (51).

On the other hand, on comparing the hemodynamic, respiratory and BIS changes between healthy patients and patients with special needs under GA, the mean HR and BIS values were seen to be lower during treatment in the CSN group compared to the HC group. These results have been published in the *Journal of Clinical and Experimental Dentistry*. These data are in contradiction with the observations of Malhotra et al. (19), who found no significant differences in hemodynamic parameters on comparing midazolam/ketamine in combination versus dexmedetomidine (19). These

discrepancies may be due to multiple causes, such as different depths of sedation, the different drugs employed, the younger age of the patients in the study published by Malhotra et al. (19) (3-6 years), or differences between the healthy pediatric patients in their study and our own study group in which the patients had mental disorders that could be accompanied by other systemic conditions capable of influencing HR and BIS. In this regard, it must be remembered that cardiac alterations are found in some of the syndromes present in the CSN group (Down syndrome, Cayler syndrome and Turner syndrome).

The variables BP, RR, SaO_2 and exhaled CO_2 behaved slightly differently in the two groups, but there were no statistically significant differences over treatment time. Saravia et al. (49) did not measure CO_2, but recorded fluctuations in HR and SBP and DBP during treatment under sedation. They associated these changes to environmental stimuli, though no significant variations were observed between the pre- and intraoperative recordings. The mentioned authors found 41% of the sedated patients to develop mild hypoxia and 6% moderate hypoxia during sedation (49); this is in contrast to the findings of our own study, where none of the patients presented hypoxia episodes.

Regarding BIS, the lowest values observed in the present study corresponded to the CSN group, employing the same dose of anesthetic drug. It could be postulated that the age of the patients might influence the BIS data (17,52), as observed by Bannister et al. (53), who assessed the effect of the anesthetic upon the BIS values in children under GA, affirming that the results differ according to the age of the patient group involved.

Previous studies have found the BIS pattern in cerebral palsy (52) and in mentally retarded children (autism, cerebral palsy and Down syndrome) (54) to follow the same trend as in normal patients during GA in dentistry. This is in contrast to our own findings, since the BIS scores in the CSN group were significantly lower than in the HC group. Our results are in concordance with those reported by Choudhry and Brenn (52).

Likewise, Valkenburg et al. (55) found the BIS values to be significantly lower in intellectually disabled children compared with controls in percutaneous endoscopic gastrostomy performed under general anesthesia. According to the mentioned authors, these lower values possibly could be explained by the fact that some brain disorders may exhibit epileptiform or non-epileptiform forms, or need anticonvulsant medication.

In line with other investigations, BIS monitoring has been used efficiently and effectively in mentally retarded patients (56,57), and could have a positive effect upon the recovery profile in developmentally delayed pediatric patients (57).

As we have seen in our systematic review, the use of BIS in intravenous sedation allows us to evaluate sedation levels objectively (17,35) and in real time (17,39,46), eliminating the need for clinical evaluation (17). This is very important in the field of dentistry, since the presence of intraoral instruments makes it difficult to communicate with the patient to assess the level of sedation (17).

The evaluating scales have a major limitation in that they are based on subjective judgment of the clinician (16,20,39,45,58). This is particularly relevant in the context of intraoral procedures, as the patient is unable to respond adequately to verbal stimuli (35,45,58).

The BIS value is inversely correlated to the depth of sedation; accordingly, a drop in BIS value represents a deeper level of sedation (17). In this way, BIS differentiates between deep sedation and lighter levels of sedation, but runs into difficulties in distinguishing between moderate and deep sedation (17,35) - such distinction requiring a certain level of clinical experience (17).

Another advantage of BIS monitoring reported by some investigations (11,21,45) is a general reduction in the incidence of complications when BIS is used. Although GA is a safe procedure, postoperative dental morbidity or complications have been described (15). Side effects associated to sedative drugs have been reported, such as hypoxia, nausea, vomiting or tachycardia

(4,38,47,49), or allergic reactions to some of the agents used to perform GA (59). Additionally, anesthetic agents are associated with some hazards and risks to overall patient health, with some reports of morbidity and mortality (60).

Muñoz-Garcia et al. (21) found that the use of BIS monitoring led to a 30% decrease in intravenous sedative consumption, reducing the probability of secondary effects, and reducing the economic cost of the procedures (21). These observations concur with those of Sandler et al. (39). Although not all the reviewed studies mention complications associated with sedation / anesthesia (14,16,18,22,36,41,43,44), the most serious complications during oral treatment are associated with respiratory depression and hypoxemia (45), followed by nausea and vomiting (21). Bradycardia or persistent postoperative drowsiness can also be an important complication (39). The incidence of complications in the studies under review was 1.82%. The most common problem was dizziness (26.66%) (43,45) and bradycardia (26.66%) (39,43), SaO_2 < 90% (20%) (21,45), agitation (13.33%) (43), and drowsiness (6.66%) (39) and laryngospasm (6.66%) (35). Eshghi et al. (38) reported nausea and vomiting but did not specify the number of cases presenting these complications.

No intra- or postoperative complications were recorded in our study when we compared HC versus CSN in dental treatment under GA. In line with the study of Pecci-Lloret et al. (15), we likewise recorded no side effects during the study on comparing hemodynamic changes with GA or LA during dental treatment in pediatric patients. In a similar manner, Caputo et al. (61) showed mortality in patients with special needs to be minimal, and morbidity was limited to minor events. Nevertheless, side effects may occur during these procedures (postextubation croup, intraoperative wheezing and bradycardia)(62), and despite the low incidence of adverse outcomes from GA in the dental office setting, treatment should be safely and efficiently completed by well trained professionals following established protocols and guidelines (15,62).

Despite the advantages of BIS monitoring reported by some authors, its use remains controversial for others. One of its disadvantages in the field of dentistry is that the sensor of the device is place on the patient forehead, close

to the working area, and this may easily cause interferences in muscular activity or distortion of the BIS readings as a result of the use of high-frequency electrical apparatuses (18,21). While the most recent BIS monitors have been designed to eliminate the majority of artifacts, further research is still needed to obtain firm data (21). Some authors consider that BIS monitoring does not offer any advantage over the traditional methods used for sedation assessment, and that it should not be relied upon as the sole means for assessing the level of intravenous sedation (4,22,45). Another factor to bear in mind is the cost per patient of the BIS electrode, which varies from manufacturer to manufacturer between 15-40 USD (17).

In the present review, two studies provided numerical data registered by BIS (38,43), affording a quantitative measure of the levels of sedation induced, without the need to stimulate the patient (43). In agreement with Cheung et al. (45), who recommend a BIS value of between 65-85, the patients in these two studies (38,43) remained under moderate or deep sedation, presenting mean BIS values of 70.64 (38,43). The minimum BIS value registered was 38.05 (38) (ketamine group at 45 minutes into the intervention), which corresponds to the BIS range indicating a deep hypnotic state close to general anesthesia (18), while the recorded maximum value of 92.48 (43) (dexmedetomidine at group 45 minutes into the intervention) indicates minimum sedation or anxiolysis (36).

Taniyama et al. (44) found the BIS value to gradually decrease to 80-85 at the time of optimal sedation, in coincidence with Mishra (43), who showed the tested drugs to have an optimal sedative effect and induce adequate sedation levels. But these results are in contrast to the data published by Morse et al. (22), who found that the BIS value did not vary significantly from baseline to the end of the dental procedure, remaining at around 90 - a finding that places the efficacy and usefulness of BIS monitoring in some doubt.

The present review recorded a drop in mean BIS value at 25 minutes into the procedure to 69.62 (deep sedation), regardless of the sedative drug employed, and from which the patient began to recover after 45 minutes, close to the end of the treatment. In 10 articles, the authors presented the registered BIS values

as graphs, making it impossible to extract precise values for analysis (4,16,18,21,22,35,39,40,44,45). Six articles described BIS monitoring but without supplying numerical data or even expressing the values in graph format (1,14,6,41,42,63). This imposed a limitation on the present review in terms of data analysis that could preclude the drawing of firm conclusions.

Another aspect to consider is when uncooperative patients are subjected to GA. They require a greater number of dental treatments (many times, and the oral disorders they present are extensive due to delays in visiting the dentist). Given an equal number of treatments to be carried out on a patient, multiple and briefer sessions are preferred in collaborating patients so that they do not get tired and maintain their cooperation.

Lastly, some questions and limitations arise from our studies. Although the literature on the use of BIS in dentistry is increasing, the majority of studies have been conducted in adults. In this regard, data referred to adults might not be applicable to the pediatric population (52).

Furthermore, the literature offers less information about the validity of BIS monitoring in the case of children with systemic diseases or with neuronal disorders, since a low value could be attributed to brain disease or to medication taken by the patient (e.g., anticonvulsants). The available literature on the behavior of cardiopulmonary parameters in dentistry and under general anesthesia involving pediatric patients is also limited.

Apart from above, the small number of individuals included in our studies may appear to be a clear limitation. It has been very challenging to recruit a sufficient number of *a priori* vulnerable subjects and to obtain parental consent to accept treatment under general anesthesia. Nevertheless, the number of patients recruited was sufficient to find statistically significant differences, and recent evidence suggests that parental satisfaction with dental treatment under GA has increased in recent years and that it is now accepted more favorably than other active or passive behavioral management techniques (16). Furthermore, GA ensures that the child receives effective pain control, and professionals do

not need to be concerned about adequate patient cooperation (60). It undoubtedly takes an extra effort on the part of the dental professionals to make the advantages of this treatment modality understood by pediatric patients lacking cooperative ability and who are very anxious. To meet future expectations, attempts should be made to match the two study groups so that age shows no statistically significant differences, and determine whether neuronal maturation affects the BIS values and would allow us to better understand the behavior of the vital constants in both groups. Homogenizing mental diseases within the sample as far as possible and taking into account that other systemic disorders may be present in certain mental syndromes would facilitate the evaluation of their impact upon the BIS values and vital signs. Lastly, and considering the small changes recorded in some of the study parameters, a larger sample size would also be advisable in future investigations.

7. Conclusions

Main conclusion

Dental treatment under BIS monitoring affords greater safety in relation to the doses of drugs used, and also reduces the number of complications. General anesthesia improves patient satisfaction and increases their willingness to accept other treatments in the future.

Conclusions to paper I: Systematic review

Bispectral monitoring of conscious sedation offers better safety, particularly when intravenous sedation techniques are applied in a non-hospital operating room setting.

Using BIS monitoring as an everyday working tool to manage patient level of consciousness might increase the efficiency of anesthesia, and probably reduce the incidence of complications.

Nevertheless, further research in the field of dentistry is needed to confirm these advantages and to overcome the limitations identified in the studies analyzed in this review.

Conclusions to paper II: Clinical study

Propofol and sevoflurane administration allows dental treatment to be performed safely in children with special needs who otherwise would not be treated.

These drugs induce a significant decrease in heart rate and bispectral values in children with special needs versus healthy children.

Blood pressure, oxygen saturation and exhaled carbon dioxide showed similar results in both groups.

Conclusions to paper III: Clinical study

General anesthesia seems to afford more favorable cardiovascular parameters during the dental treatment process versus local anesthesia alone in pediatric patients, showing a significant lower systolic and diastolic blood pressure, and heart rate. In addition, it allows dental treatment to be performed on healthy, lacking cooperative ability children who could not be treated with local anesthesia alone.

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frequent during procedures in the maxillary anterior region. J Oral Maxillofac Surg. 2013;71:e158-163.

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9. Paper I

Evaluation of endovenous sedation using BIS monitoring in dentistry. A systematic review.

Med Oral Patol Oral Cir Bucal, 2020

Title: Evaluation of endovenous sedation using BIS monitoring in dentistry. A systematic review.

Authors:

Silvia Pérez-García. DDS, MS. International Master in Oral Surgery. Department of Oral and Maxillofacial Surgery. International University of Catalonia, Spain.

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Journal: Medicina Oral Patología Oral Cirugía Bucal (Med Oral Patol Oral Cir Bucal)

Abstract:

Background: The aim of the present review was evaluate the utility and validity of the Bispectral Index (BIS) in dental treatment carried out under endovenous sedation, and compare its efficacy with clinical sedation scales. Material and Methods: Electronic and manual literature searches were conducted by two independent reviewers for articles published up to April 2017 in several databases, including Medline and Cochrane Library. Results: Sixteen articles met the inclusion criteria. A correlation was identified between BIS and clinical sedation scales. A BIS range between 75 and 84 showed a high probability of corresponding to an Observer's Assessment of Alertness and Sedation Scale (OAA/S) value of 3; a scored 3 on the Ramsay scale corresponds around 85 on the BIS; while BIS values between 57 and 64 corresponded to a University of Michigan Sedation Scale value of 3. BIS monitoring provides continuous measurement of the patient's hypnotic state or state of consciousness, awareness, and recall. It proved impossible to perform an analysis of statistical data drawn from the studies reviewed due to the disparity of inclusion criteria among the works. Conclusions: BIS for sedation monitoring might make

possible to evaluate sedation levels objectively in real time, reducing the dose of the sedative required, increasing safety, and minimizing secondary effects.
URL: http://www.medicinaoral.com/medoralfree01/aop/22884.pdf

10. Paper II

Hemodynamic and ventilatory changes in pediatric patients with special needs: a comparative clinical study

J Clin Exp Dent, 2022

Title: Hemodynamic and ventilatory changes in pediatric patients with special needs: A comparative clinical study.

Authors:

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Journal: Journal of Clinical and Experimental Dentistry (J Clin Exp Dent)

Abstract: Background: Very limited data are available on the hemodynamic and ventilatory changes during sedation and general anesthesia using bispectral index (BIS) monitoring in intellectually disabled children. The purpose was to determine the hemodynamic and ventilatory changes after propofol and sevoflurane administration in children with special needs (CSN) versus healthy children (HC) during dental treatment.

Material and Methods: Forty pediatric patients needing dental treatment were allocated into two groups: children without systemic disease (healthy children [HC]) and mentally disabled children (children with special needs [CSN]). Sevoflurane in oxygen (100% oxygen, 5 l/min) and continuous propofol infusion (target-controlled infusion [TCI], 2 µg/ml) were used as sedative agents, and 2% lidocaine with 1:80,000 adrenaline was used as local anesthesia in both groups. Heart rate (HR), oxygen saturation (SaO2), respiratory rate (RR), exhaled

carbon dioxide (CO2), blood pressure (BP) and bispectral monitoring (BIS) values were recorded during the entire dental treatment procedure.
Results: A statistically significant decrease in systolic BP, diastolic BP and RR was observed, with no significant differences between the healthy and disabled groups. In contrast, the HR and BIS values were lower in the CSN group than in the healthy patients ($p \leq 0.05$).
Conclusions: Patients with special needs had lower HR and BIS values than healthy patients, while BP, SaO2 and exhaled CO2 showed similar results in both groups.
URL: http://www.medicinaoral.com/medoralfree01/aop/59951.pdf

11. Paper III

Comparison of hemodynamic changes with general or local anesthesia during dental treatment in pediatric patients: a prospective clinical study.

Spec Care Dentist, 2023

Title: Comparison of hemodynamic changes with general or local anesthesia during dental treatment in pediatric patients: A prospective clinical study

Authors:

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Journal: Special Care in Dentistry (Spec Care Dent)

Abstract:

Background and aim: Severe hemodynamic fluctuations during dental treatment can trigger highly undesirable physical reactions. A study was made to determine whether the administration of propofol and sevoflurane contributes to the stabilization of hemodynamic parameters during dental treatment in pediatric patients versus the use of local anesthesia alone.

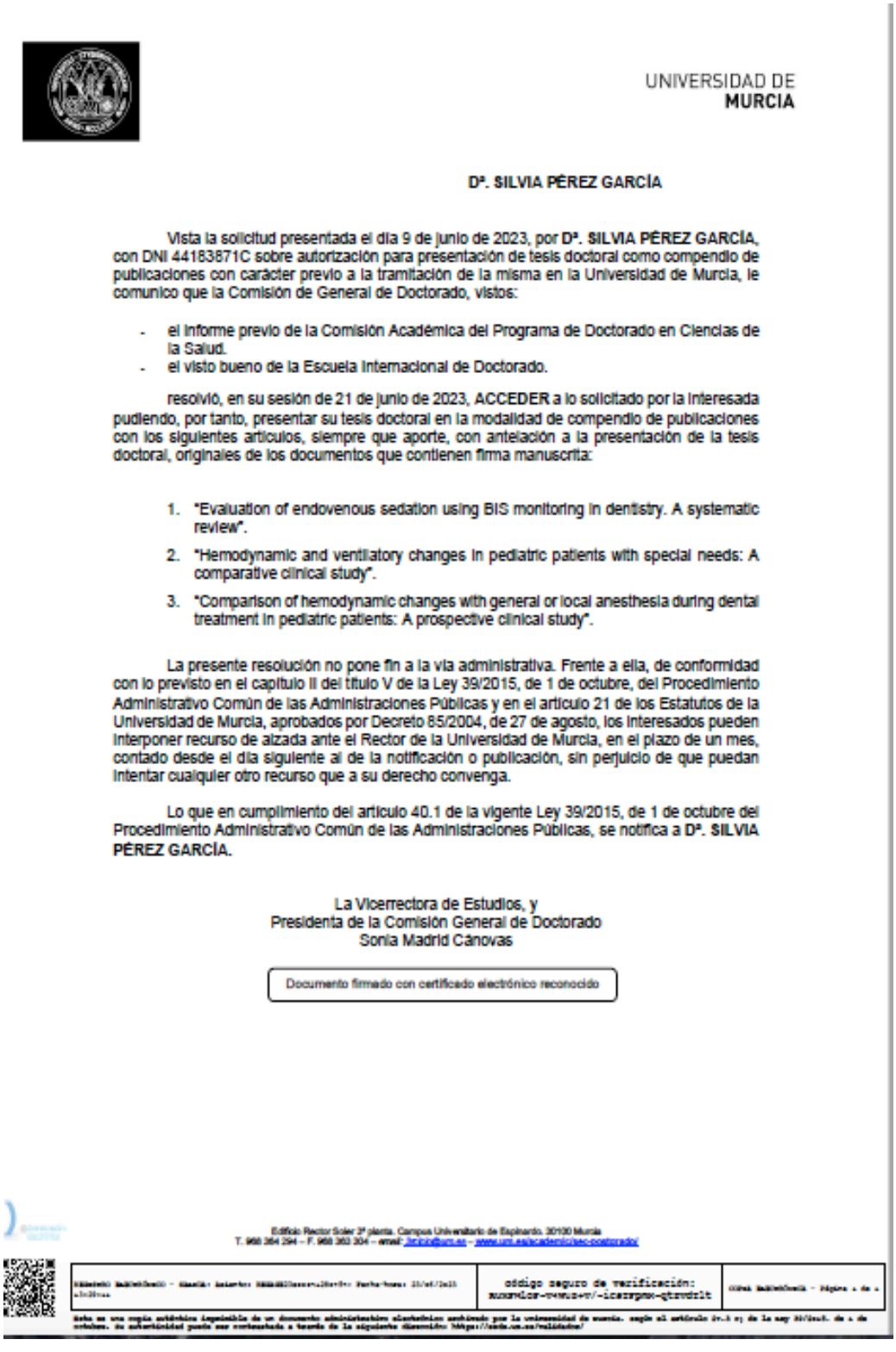
Materials and methods: Forty pediatric patients needing dental treatment were assigned to either general anesthesia with local anesthesia (study group [SG]) or local anesthesia alone (control group [CG]). Two percent sevoflurane in oxygen (100% oxygen, 5 L/min) and continuous propofol infusion (target controlled infusion [TCI], 2 μg/mL)were used as general anesthesia agents in SG; and 2% lidocaine with 1:80,000 adrenaline was used as local anesthesia in both groups. Heart rate, blood pressure and oxygen saturation were measured before starting dental treatment (baseline) and every 10 min during dental treatment.

Results: Blood pressure ($p < .001$), heart rate ($p = .021$) and oxygen saturation ($p = .007$) decreased substantially after the administration of general

anesthesia. The levels of these parameters subsequently remained low and then recovered at the end of the procedure. On the other hand, the oxygen saturation values remained closer to baseline in SG versus CG. In contrast, the hemodynamic parameters experienced lesser fluctuations in CG than in SG.
Conclusions: General anesthesia affords more favorable cardiovascular parameters during the entire dental treatment in comparison to local anesthesia alone (blood pressure and heart rate decrease significantly and oxygen saturation proves more stable and with values closer to baseline), and allows dental treatment to be performed on healthy, lacking cooperative ability children who otherwise could not be treated with local anesthesia alone. No side effects were observed in either group.
URL: https://onlinelibrary.wiley.com/doi/abs/10.1111/scd.12890

12. Annexes

Authorization of the general doctoral commission of the UM to present the Ph.D. dissertation in the modality of completion of publications



UNIVERSIDAD DE
MURCIA

Dª. SILVIA PÉREZ GARCÍA

Vista la solicitud presentada el día 9 de junio de 2023, por **Dª. SILVIA PÉREZ GARCÍA**, con DNI 44183871C sobre autorización para presentación de tesis doctoral como compendio de publicaciones con carácter previo a la tramitación de la misma en la Universidad de Murcia, le comunico que la Comisión de General de Doctorado, vistos:

- el informe previo de la Comisión Académica del Programa de Doctorado en Ciencias de la Salud.
- el visto bueno de la Escuela Internacional de Doctorado.

resolvió, en su sesión de 21 de junio de 2023, **ACCEDER** a lo solicitado por la interesada pudiendo, por tanto, presentar su tesis doctoral en la modalidad de compendio de publicaciones con los siguientes artículos, siempre que aporte, con antelación a la presentación de la tesis doctoral, originales de los documentos que contienen firma manuscrita:

1. "Evaluation of endovenous sedation using BIS monitoring in dentistry. A systematic review".
2. "Hemodynamic and ventilatory changes in pediatric patients with special needs: A comparative clinical study".
3. "Comparison of hemodynamic changes with general or local anesthesia during dental treatment in pediatric patients: A prospective clinical study".

La presente resolución no pone fin a la vía administrativa. Frente a ella, de conformidad con lo previsto en el capítulo II del título V de la Ley 39/2015, de 1 de octubre, del Procedimiento Administrativo Común de las Administraciones Públicas y en el artículo 21 de los Estatutos de la Universidad de Murcia, aprobados por Decreto 85/2004, de 27 de agosto, los interesados pueden interponer recurso de alzada ante el Rector de la Universidad de Murcia, en el plazo de un mes, contado desde el día siguiente al de la notificación o publicación, sin perjuicio de que puedan intentar cualquier otro recurso que a su derecho convenga.

Lo que en cumplimiento del artículo 40.1 de la vigente Ley 39/2015, de 1 de octubre del Procedimiento Administrativo Común de las Administraciones Públicas, se notifica a **Dª. SILVIA PÉREZ GARCÍA.**

La Vicerrectora de Estudios, y
Presidenta de la Comisión General de Doctorado
Sonia Madrid Cánovas

Documento firmado con certificado electrónico reconocido

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código seguro de verificación:
[illegible]

Report of the directors of the Ph.D. dissertation

INFORME DE LOS DIRECTORES JUSTIFICATIVO DE LA PRESENTACIÓN DEL COMPENDIO DE PUBLICACIONES COMO TESIS DOCTORAL

DOCTORANDA: Dª. Silvia Pérez García, con DNI 44183871C

TÍTULO DE LA TESIS DOCTORAL: HEMODYNAMIC, VENTILATORY AND BIS MONITORING CHANGES IN PEDIATRIC DENTISTRY
Cambios hemodinámicos, ventilatorios y de la monitorización con BIS en Odontología pediátrica

DATOS DE LOS CODIRECTORES DE TESIS:

Dr. D. Jordi Gargallo Albiol, con DNI 35099748T
Dr. D. Juan Antonio Ruiz Roca, con DNI 23009025D

ARTÍCULOS QUE CONFORMAN LA TESIS DOCTORAL PRESENTADA COMO COMPENDIO DE PUBLICACIONES:

Artículo 1. EVALUATION OF ENDOVENOUS SEDATION USING BIS MONITORING IN DENTISTRY
Artículo 2. HEMODYNAMIC AND VENTILATORY CHANGES IN PEDIATRIC PATIENTS WITH SPECIAL NEEDS: A COMPARATIVE CLINICAL STUDY
Artículo 3. COMPARISON OF HEMODYNAMIC CHANGES WITH GENERAL OR LOCAL ANESTHESIA DURING DENTAL TREATMENT IN PEDIATRIC PATIENTS: A PROSPECTIVE CLINICAL STUDY

D. Jordi Gargallo Albiol y D. Juan Antonio Ruiz Roca como codirectores de la tesis de la doctoranda Silvia Pérez García exponen que:

La doctoranda es autora de los artículos que conforman la tesis doctoral como compendio de publicaciones.
Todos los artículos han sido aceptados con fecha posterior a la presentación del proyecto de tesis de la doctoranda.
Los artículos han sido aceptados y publicados en revistas indexadas en Pubmed en la categoría de Q2.
Los artículos que conforman la tesis como compendio tienen un valor científico por sí mismos, y configuran una unidad científica. Todos ellos son resultados originales de la investigación de la doctoranda.

SRA. PRESIDENTA DE LA COMISIÓN GENERAL DE DOCTORADO. UNIVERSIDAD DE MURCIA.

La tesis doctoral concluye la actividad investigadora realizada por la doctoranda durante sus estudios de doctorado, realizados con excelentes niveles de dedicación y aprovechamiento, demostrando haber logrado una

preparación y nivel de competencia suficientes para poder optar al grado de doctor.

Por tanto, y para que así conste y surta los efectos oportunos, el presente documento es firmado por los codirectores de la tesis doctoral (Dr. Jordi Gargallo Albiol y Dr. Juan Antonio Ruiz Roca) como justificación y autorización de la presentación de la tesis por parte de la doctoranda Silvia Pérez García como compendio de publicaciones.

En Murcia, a 9 de Junio de 2023

Fdo. Co-director de la tesis
Dr. Jordi Gargallo Albiol

Fdo. Co-director de la tesis
Dr. Juan Antonio Ruiz Roca

Fdo. Doctoranda
Dª. Silvia Pérez García

Ethical Committee of Investigation

UNIVERSIDAD DE MURCIA | Vicerrectorado de Investigación

CEI Comisión de Ética de Investigación

CAMPUS MARE NOSTRUM

INFORME DE LA COMISIÓN DE ÉTICA DE INVESTIGACIÓN DE LA UNIVERSIDAD DE MURCIA

Emilio Ginés Martínez Navarro, Catedrático de Universidad en funciones de Secretario de la Comisión de Ética de Investigación de la Universidad de Murcia

CERTIFICA:

Que Dª. Silvia Pérez García ha presentado la Tesis Doctoral titulada *"Monitorización de la sedación con BIS en Odontología"*, dirigida por el Dr. D. Jordi Gargallo Albiol, la Drª. Dª. María Pía López Jornet y el Dr. D. Juan Antonio Ruiz Roca, a la Comisión de Ética de Investigación de la Universidad de Murcia.

Que dicha Comisión analizó toda la documentación presentada, y de conformidad con lo acordado el día 24 de abril de 2017[1], por unanimidad, se emite INFORME FAVORABLE, desde el punto de vista ético de la investigación.

Y para que conste y tenga los efectos que correspondan, firmo esta certificación, con el visto bueno del Presidente de la Comisión

Vº Bº
EL PRESIDENTE DE LA COMISIÓN
DE ÉTICA DE INVESTIGACIÓN DE LA
UNIVERSIDAD DE MURCIA

Fdo.: Antonio Juan García Fernández

Firmado con certificado electrónico reconocido.
La información sobre el firmante, la fecha de firma y el código de verificación del documento se encuentra disponible en los márgenes izquierdo e inferior.

ID: 1459/2017

[1] A los efectos de lo establecido en el art. 19.5 de la Ley 40/2015 de 1 de octubre de Régimen Jurídico del Sector Público (B.O.E. 02-10), se advierte que el acta de la sesión citada está pendiente de aprobación

código seguro de verificación: muxrmjws-xayrotzp-iriJpe7l-8k/mosgp