Efficacy of a premedication with melatonin during cataract surgery under peribulbar block: a prospective randomized double-blinded study

Mélatonine en prémédication pour la chirurgie programmée de la cataracte : étude prospective randomisée en double aveugle

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Abstract

Introduction: Cataract is a ubiquitous pathology. Its prevalence increases with age. Nowadays, cataract surgery is increasingly performed on an outpatient basis under locoregional anesthesia. In this context, sedation-analgesia is essential but not without risks.

Aim : To evaluate the effectiveness of premedication with melatonin on intraoperative sedation-analgesia.

Methods: This is a prospective randomized double-blind study including patients proposed for scheduled cataract surgery by phacoemulsification under peribulbar anesthetic block. The participants will be randomized into two groups: group (M) will receive 05 tablets of melatonin (10mg sublingual) and group (P) will receive 05 tablets of Sucralose sublingually. Perioperative sedation-analgesia will be evaluated by the Ramsey score, the bisectral index, the simple verbal scale (EVS) and by the perioperative consumption of midazolam and alfentanyl. Secondary endpoints will be the degree of preoperative anxiety (Amsterdam Preoperative, Anxiety and Information Scale), the perioperative tonus of the eyeball, intraoperative nicardepine consumption and patients and surgeons satisfaction. A value of $p<0.05$ will be considered statistically significant.

Expected Results: The administration of melatonin as a premedication for scheduled cataract surgery will allow a better quality of intraoperative sedation-analgesia, a reduction in the doses consumed of midazolam and alfentanyl, improves surgical conditions, leads to a decrease in ocular tone, and optimizes surgical safety conditions for the patient.

Key words: melatonin, premedication, cataract, phacoemulsification, sedation-analgesia, peribulbar block, loco regional anesthesia.

Résumé

Introduction : La cataracte est une pathologie ubiquitaire dont la prévalence augmente avec l'âge. De nos jours, la chirurgie de la cataracte est de plus en plus pratiquée en ambulatoire sous anesthésie locorégionale. Dans ce contexte, la sédation-analgésie per opératoire est essentielle mais non dénuée de risques.

Objectif : Evaluer l'efficacité de la prémédication par la mélatonine sur la sédation-analgésie de confort per opératoire.

Méthodes : Etude prospective randomisée en double aveugle incluant des patients proposés pour une chirurgie programmée de la cataracte par phacoémulsification sous bloc anesthésique péri bulbaire. Les patients seront répartis en deux groupes : groupe (M) recevront 05 comprimés de mélatonine soit 10mg en sublingual et groupe P recevront 05 comprimés de Sucralose en sublingual. La sédation-analgésie péri opératoire, sera évaluée par le score de Ramsey, l'index bisectral, par l'échelle verbale simple (EVS) de la douleur et par la consommation périopératoire de midazolam et d'alfentanyl. Les critères de jugement secondaire seront le degré d'anxiété préoperatoire (Amsterdam Preoperative, Anxiety and Information Scale), le tonus oculaire péri opératoire, la consommation de nicardipine en per opératoire et le degré de satisfaction des patients et des chirurgiens. Une valeur de $p<0.05$ sera considérée statistiquement significative.

Résultats attendus : L'administration de la mélatonine en prémédication pour une chirurgie programmée de la cataracte permettra une réduction des doses consommées en hypnotiques et en morphinomimétiques, améliorera les conditions chirurgicales, entraînera une baisse du tonus oculaire et optimisera les conditions de sécurité opératoire pour le patient.

Mots clés: mélatonine, prémédication, cataracte, phacoémulsification, sédation-analgésie, bloc péribulbaire, anesthésie locorégionale.

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INTRODUCTION

Cataract is defined as partial or total opacification of the lens responsible for a progressive decrease in visual acuity (1). It is a ubiquitous pathology (2). In 2017, cataract affected 95 million of people worldwide (1). Its prevalence in the world continues to increase due to the aging of the population (2). It was 3-9% at the age of 55-64 years and 92.6% at the age of 80 years and over (2). It is the second most common cause of severe visual impairment after uncorrected refractive disorders and is the leading cause of blindness in underdeveloped and developing countries (1). Its treatment requires the surgical insertion of an intraocular lens after removal of the opacified lens. In 2021, cataract surgery was the most common surgery not only in ophthalmology, but also in all surgical specialties (3). It is most often performed on an outpatient basis with a prevalence of approximately 20 million cases per year worldwide (3). In France, approximately 800 000 procedures of this type are performed each year (4). Cataract surgery has evolved over the last few years from intra capsular extraction of the opacified lens, to extra capsular extraction of the lens, and then to phacoemulsification (1). Phacoemulsification with implantation of an intraocular lens in the capsular bag has become the reference procedure in the surgical treatment of cataract. This technique of surgery offers excellent anatomical, visual and functional results with the lowest complication rate (3). It also, reduces the number of falls, contributes to the improvement of cognitive performance and to the well-being of the elderly on a daily basis (5, 6). To perform this surgery, the anesthetic technique can be either general anesthesia, locoregional anesthesia or topical anesthesia (7). The general anesthesia technique in an elderly population with cardiovascular risk factors exposes these patients to a significant postoperative morbidity (7, 8). Nowadays, this anesthetic technique is less and less used (7). Its indication is more and more limited to the profile of loco-regional anesthesia techniques which seem to have many advantages: simple and effective; safe and easy to perform; less morbid; more affordable and less costly (9, 10). Two types of anesthetic blocks of the eyeball can be performed depending on whether the injection of the local anesthetic solution is intra or extra conical: the retrobulbar block or the peribulbar block (7, 8). These anesthetic blocks often require sedation-analgesia in order to avoid the patient's pain and discomfort linked to the puncture of the eyeball (10, 11). This comfort sedation-analgesia generally associates the intravenous administration of rapid hypnotic and or morphinomimetics agent having short delay and duration of action (10, 11). During this surgery, some operative procedures are also associated with intense pain, notably manipulation of the iris, aspiration, irrigation and lens implantation (12). This intra operative pain can be the cause of several undesirable effects, such as the occurrence of bradycardia due to an oculo-cardiac reflex, arterial hypertensive peaks, elevation of intra-ocular pressure, expulsion of the implant, or anxiety that can lead to psychomotor agitation, thus hindering the surgery from going smoothly (13). In this context, an additive sedation-analgesia is often necessary. It aims to ensure anxiolysis, analgesia and somnolence without loss of patient's cooperation and verbal communication and then, improve the comfort of the patient and the surgeon (14, 15).

However, the clinical practice of sedation-analgesia, during operative procedures under loco-regional anesthesia, is not without risks (15). In some cases, it can be hazardous and even harmful for the patients. It can be the cause of respiratory depression, hypoxia with deep arterial desaturation, loss of consciousness, nausea and or vomiting, lack of cooperation from the patient, or even paradoxical agitation and threaten the outcome of the surgery and the patient (15, 16).

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone secreted by the pineal gland. It has several physiological functions: regulation of circadian rhythm and sleep, it also regulates the reproductive axis, anxiety and intraocular pressure; it has an antioxidant activity, an analgesic action via gabaergic receptors and receptors located on the dorsal horn of the spinal cord (17, 18). It is considered a harmless drug. It is used for the treatment of sleep disorders, to potentiate the analgesic effect of certain drugs and for the premedication of patients. Many studies demonstrated that preoperative oral melatonin used for premedication was effective to reduce perioperative anxiety, to enhance pain control, to increase levels of sedation without impairment of cognitive and psychomotor skills or affecting the quality of recovery (19). Melatonin was used in many types of surgery such as gynecologic procedures, knee arthroscopic surgeries, laparoscopic cholecystectomy, elective prostatectomy, lumbar laminectomy and during intravenous regional anesthesia procedures (20). In children, melatonin was effective during diagnostic procedures requiring sedation or general anesthesia such as magnetic resonance imaging, auditory brainstem response tests and encephalogram (21). Recently, a hypnotic effect of melatonin similar to those of propofol or thiopental, when administred as premedication have been demonstrated (16). Different doses of melatonin were used for premedication (20). When given orally, its peak plasma concentration is reached after 60 minutes with an elimination half-life of up to 120 minutes (22, 23). The common specific characterization to point out in all these studies is that significant short and long term side effects after oral administration of standard and high doses up to 20 mg of melatonin have not been reported (21).

The objective of this prospective randomized double-blinded study is to evaluate the effectiveness of melatonin premedication on the quality of intra operative sedation-analgesia during cataract surgery.

METHODS

Our study has been approved by the local ethics committee and has been registered in the PanAfrican Clinical Trial Registry data base (*PACTR202210764449003*). It is a prospective randomized double-blind study that will be carried out by the department of anesthesia and surgical resuscitation of the Farhat HACHED university hospital of Sousse, Tunisia. Our work will be spread over a period of 45 days. We will recruit patients admitted to the operationg room of the ophthalmology department for scheduled cataract

surgery by phacoemulsification performed under peribulbar anesthesia block. The inclusion criteria of our study are: oral and written informed consent of the patients; an age over 50 years old; an ASA class I, II, III; a cataract of senile origin, a cataract complicating an ophthalmological pathology such as uveitis or pigmentary retinopathy, a cataract complicating an extra-orbital pathology such as diabetes, chronic inflammatory diseases and hypoparathyroidism; a post-traumatic cataract; a cataract of iatrogenic origin following long-term corticosteroid therapy or orbital radiation therapy. This study will exclude patients with a history of acute or chronic alcohol consumption or having caffeine-containing beverages during the last 24 hours, a psychiatric history; a history of long-term use of sedatives, anxiolytics or analgesics; a history of complications from ophthalmic surgery; sleep disorders; cognitive or sensory disorders; congenital cataract (embryopathies or hereditary); cataract secondary to genetic diseases such as Trisomy 21 or Steinert's dystrophy; a secondary cataract on implant following a posterior capsular opacification; a strong myopia staphyloma; a glaucoma in the controlateral eye; a contraindication of the use of melatonin; a contraindication to loco-regional anesthesia; any indications to convert to general anesthesia such as failure of loco-regional anesthesia technique; failure to comply with the 60-minute premedication period or a surgical procedure that has exceeded the half-elimination time of melatonin (120 minutes); patients with an intra operative anesthetic complications; patients with intra operative surgical complications such as an expulsive hemorrhage of the eyeball, rupture of the capsule with vitreous exit, capsular or zonular rupture, or a non compliant implant. During the pre-anesthetic visit, an anesthesiologist will collect oral and written informed consent of the patients after explaining: the modalities of administration of melatonin or placebo, the scores of anxiety, pain evaluation, personal satisfaction and psychomotor function evaluation tests (Trieger Dot Test and word memorization test). The patients will be randomized into two groups (www.randomizer.org): the Melatonin group (Group M) will receive a dose of *10 mg of Melatonin by* sublingual route, that is to say 05 tablets of 2 mg (**DorZen**® *Xen laboratories La Chotrana Tunisia*); the placebo group (Group P) will receive ***a placebo*** by sublingual route, that is to say 05 tablets of sucralose (*Swity® NOVALAB laboratories La Soukra Tunisia*). All the study drugs will be prepared by the hospital pharmacy and a code number will be assigned to each envelope. On the morning day of the surgery, one or the other of the two medications, contained in a sealed envelope, will be administered to the patients, 60 minutes before the operation by a nurse not involved in the study. Thereafter, the participants will be placed in a quiet and dimmed light area until they enter the operating room. In the operating theater, neither the anesthesia nor surgery team in charge of the patient will be informed of the premedication protocol taken by the patient. All patients will be placed confortably on the operating table in the supine position. Monitoring's patient will include the 3-lead electrographic trace, pulsed oxygen saturation, capnography curve, non-invasive blood pressure, and sedation by the Bispectral index™ *(Bispectral index™-BISTM Monitoring system*, *Covidien Products, United States of America*). A 20-gauge peripheral venous line will be placed and a 0.9% isotonic saline solution will be administered. An oxygen face mask, with an O2 flow rate 4L/min, equipped with a CO2 sensor will be implemented before any sedation and until the end of the operation. After checking the side of the eye to be operated on, a few drops of a local contact anesthetic (*Oxybrupocaïne 0.4 % (CEBESINE®0.4%*)) will be applied to ensure anesthesia of the conjunctiva and the cornea. The periorbital skin will be disinfected with a *Betadine®* solution. At the time of the peribulbar anesthetic block, all patients will be sedated with a combination of a hypnotic *Midazolam* (HYPNOVEL®) at a dose of *0.02 mg/kg* and a morphinomimetic *Alfentanyl* (RAPIFEN®) at a dose of *3 µg/kg* intravenously administered respectively at 05 minutes and 01 minute of the induction of loco-regional anesthesia. The peribulbar block will consist of two transcutaneous injections of 2% lidocaïne according to the recommendations of the French Society of Anesthesia and intensive care (SFAR) (24).

Operative monitoring of all patients will routinely include state of consciousness, heart rate, non-invasive blood pressure, respiratory rate, capnograph (PetCO2 curve), and pulsed oxygen saturation; at the various operative times (before and after sedation, before and after loco-regional anesthesia, at 5 minutes and 15 minutes from the start of the surgery and until its end). Intraoperative sedation will be assessed by Ramsey score and ***BIS index™*** monitoring, at the time of induction of the peribulbar block, at 5 minutes, 15 minutes and at the end of the surgery. For the proper conduct of the surgery, we'll define a sedation of quality by a Ramsey score between 2 and 4. Additional doses of Midazolam (Bolus of 1mg) will be administered on demand, and/or if the Ramsey sedation score is strictly below 2 during the operation. Intraoperative analgesia will be assessed by a simple verbal scale where the patient will choose a number from 0 to 4 reflecting the severity of the pain (0: no pain, 1: mild pain, 2: moderate pain, 3: severe pain, 4: extremely severe pain). The assessment of analgesia will be noted at the time of induction of the peribulbar block, at 5 minutes, 15 minutes and at the end of the surgery. For the good progress of the operation, we will define an analgesia of quality by a simple verbal scale<2. Additional doses of Alfentanyl (Bolus 100 µg) will be administered on demand, and/or if the pain is greater than or equal to 2 on the simple verbal scale throughout the operation. The management of deep sedation (Ramsey score between 5 and 6) and /or prolonged respiratory depression (bradypnea< 10 cycles/min and deep arterial desaturation<90% for more than 05 min), will be left for the free judgment of the anesthetic team in charge of the patient in the operating room, by using ***Naloxone*** (NARCAN®) and/or *Flumazenil* (ANEXATE®) and/or recourse to a general anesthesia. At the end of the surgery, the total cumulative

dose of midazolam and alfentanyl consumed will be noted. Perioperative anxiety will be assessed by means of the *Amsterdam Preoperative, Anxiety and Information Scale* (***APAIS***) including 6 items evaluating the degree of anxiety and the patient's desire for information related to the surgery and operation. Anxiety score will be recorded during the pre-anesthetic visit and in the operating room just before induction of sedation. The measurement of intraocular pressure by a tonometer (***Perkins Tonometer®,*** *HS-UK, the United Kingdom*) will be done preoperatively during the ophthalmology consultation; in the operating room before the induction of the peribulbar block and postoperatively at H24 on the contralateral eye by an ophthalmologist not included in the study. During the operation, ***nicardipine*** (***Loxen®***) will be administered in titration at the request of the surgeon and/or to lower an arterial blood pressure > 160/90 mmHg, by direct intravenous bolus of 1 mg, in order to avoid the risk of expulsive hemorrhage of the eyeball by increasing the intraocular pressure. A local antibiotic of the second generation cephalosporin type, ***Cefuroxime*** (***Zinnat®***), will be administered in situ by the surgeon at the end of the operation. At the end of the surgery, the surgeon's satisfaction with the operating conditions will be evaluated using the Likert satisfaction scale composed of 4 items (-2: not at all satisfied, -1: dissatisfied, 1: satisfied, 2: very satisfied). In the recovery room, patient's satisfaction will be determined by the Likert scale as well as the recovery of psychomotor function by the Trieger Dot Test and the word memorization test. Perioperative adverse effects related to melatonin premedication (irritability, nervousness, agitation, headache, dizziness, nausea/vomiting) will be noted. At post-operative H2, in the absence of any medical/surgical complications, all patients will be allowed to leave the recovery room. Perioperative data will be collected on a pre-established data collection sheet, by the anesthesiologist in charge of the patient in the operating room and who does not know the type of premedication taken by the patient. The parameters collected perioprativelly will be the demographic characteristics of the participants (age; sex; BMI (weight and height); medical/surgical, anesthetic and allergy history; ASA class (American Society of Anesthesiologists); the operative indication (eye to be operated on and etiology of the cataract); the state of the perioperative anxiety (APAIS); the duration of the operative act; the total dose of Midazolam and Alfentanyl administered (induction dose and maintenance dose); the state of consciousness (Ramsey score and BIS index™); the perioperative pain (Simple verbal scale and intraoperative Alfentanyl consumption); hemodynamic status (heart rate, systolic, diastolic and mean arterial blood pressure, occurrence of an oculo-cardiac reflex); respiratory status (respiratory rate, pulsed O2 saturation). These parameters will be collected at the following times: T-1: during the pre-anesthetic visit, T0: on admission to the operating room; T1: at 01 minute of sedation induction; T2: at 05 minutes of the beginning of the surgical act; T3: at 15 minutes of the beginning of the surgical act; T4: at the end of the surgery; T5: in the recovery room. In addition, we will also note the tonus of the eyeball (perioperative intraocular pressure) at the ophthalmology consultation, at admission to the operating room and at H24 postoperative; intraoperative administration of nicardipine (Loxen®); the satisfaction of the patient and the surgeon at the end of the surgery (Likert satisfaction scale); the recovery of psychomotor function (Trieger Dot Test and the word memorization test) as well as the adverse effect of melatonin. All collected data will be validated by an investigator blinded to the randomization and then analyzed by an independent statistician (Box 1).

Box 1. Study plan

Day-7 :	Randomization sheet
Day-3 :	Code number allocation and preparation of the medication in sealed envelopes
Day 0 :	Preanesthetic visit and patient consent
Day 1 :	Premedication and first case surgery
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Day 45 :	Premedication and last case surgery
Day 46 :	Validation of the data collection sheets
Day 60 :	Data statistical analysis
Day 90 :	Results

STATISTICAL ANALYSIS

To determine our sample size, a preliminary study was conducted during a period of 30 days. It included patients admitted for scheduled cataract surgery by phacoemulsification performed under peribulbar block. The aim of this preliminary study was to determine the average total dose of midazolam and alfentanyl required to perform this type of surgery. During that period 69 patients were operated. In this cohort, to achieve sedation-analgesia mean consumption of Midazolam and Alfentanyl was respectively 1.9 ± 0.45 mg and 346 ± 112 µg. Thus, the size of our study population was calculated by assuming that premedication with melatonin would allow us to reduce the average total dose of midazolam and alfentanyl consumed during surgery by 50%. Taking into account a 1-β power at 95% and an alpha risk of error at 0.05, we had 17 patients in each group. In order to compensate for any unforeseen events, 30 patients will be recruited in each group. The description of the qualitative variables will be done by the observed numbers and frequencies (%). For the quantitative variables, the study of the distribution of the data will be done by the skewness and kurtosis coefficients and by the normality tests. The description of these variables will be done by the means and standard deviation

in case of normal distribution and by the medians and interquartile ranges in the opposite case. For the analysis of the association between two qualitative variables, we will use Pearson's chi2 test for the comparison of two frequencies if the conditions of application are verified and Fischer's test in the opposite case. For the analysis of the association between a qualitative variable and a quantitative variable, we will use the Student's t test for the comparison of two means in case of normal distribution and the Mann Whitney test in the opposite case. A p value of 0.05 will be considered significant.

EXPECTED RESULTS

Our study will allow us to demonstrate a better quality of intraoperative sedation-analgesia (Ramsey score between 2 and 4 and a simple verbal scale <2) in case of premedication with melatonin compared to the placebo group: reduction of midazolam and alfentanyl consumption during the intraoperative period. In addition, the study will demonstrate a decrease in the intra-ocular tone and less recourse to nicardipine intraoperatively; better satisfaction among patients and surgeons; the absence of repercussions of melatonin on the psychomotor recovery of patients after the surgery and the safety of using melatonin in this indication.

ETHICS CONSIDERATIONS

The study protocol was approved by the local ethics committee (***CEFMS 132/2022)***. The authors declare no conflict of interest. The products used for this research are commonly use products in our country. There is absolutely no conflict of interest between the authors and the producers of the products. We do not intend to use these products for any advertisement purposes but only for the advancement of knowledge. Also, the research will not be funded by the producing companies of the products. All medications will be sponsored by the anesthesia and intensive care department of Farhat HACHED teaching hospital.

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