JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

RESEARCH ARTICLE Open Access

Use of Sodium Fluorescein in Extrinsic Tumours in Skull Base Surgery at the National Institute of Neurology and Neurosurgery MVS

Paula Alejandra Benítez Gasca[1*], Juan Luis Gómez Amador[2], Samuel Romano Feinholz,[3] Víctor Alcocer Barradas.[3]

[1] General Hospital of Mexico (Hospital General de México)

[2] National Institute of Neurology and Neurosurgery (Instituto Nacional de Neurología y Neurocirugía)

[3] ABC Medical Center (Centro Médico ABC)

Received date: September 24, 2024, **Accepted date:** September 30, 2024, **Published date:** October 08, 2024.

***Corresponding Author:** Dr. Paula Alejandra Benítez Gasca, General Hospital of Mexico (Hospital General de México), México.

Abstract

Advances in neurosurgery have focused on improving the precision of brain tumor resections, particularly for tumors located in challenging areas like the skull base. Among the tools enhancing surgical accuracy is sodium fluorescein (FNa), a fluorophore that improves tumor visualization by highlighting cancerous tissues during surgery. This study examined the use of FNa in 16 patients with extrinsic skull base tumors at the National Institute of Neurology and Neurosurgery, utilizing the OPMI Pentero 900 Carl Zeiss Meditec microscope with a YELLOW 560 filter for intraoperative fluorescence imaging.

The results showed that FNa effectively enhanced the surgeon's ability to differentiate tumor tissue from healthy brain matter, facilitating more extensive and precise resections while reducing the risk of complications. Given its cost-effectiveness, safety, and reliability, sodium fluorescein presents a valuable tool in improving brain tumor surgery outcomes, particularly for challenging skull base tumors. Further studies are recommended to establish its widespread use in neurosurgical practices.

Keywords: Sodium fluorescein (FNa), Skull base tumors, Brain tumor resection, Neurosurgery, Intraoperative imaging, Fluorescence-guided surgery, Tumor visualization.

Introduction

Imagine exploring a thick and unfamiliar forest, where every tree and trail weave together in a natural labyrinth, how do you find your way to a specific point you wish to discover? Although instinct and knowledge of the terrain can be helpful, wouldn't itbe beneficial to have a tool that serves as a reliable guide?

Similarly, in the intricate landscape of the human brain, neurosurgeons face comparable challenges. Each brain fold and sulcus can be a labyrinth in itself, and when a lesion is hidden deep within this brain territory, surgical navigation becomes even more complex. Although surgical professionals possess a thorough knowledge of brain anatomy and vast experience in the operating room, lesions in critical areas can present real challenges, requiring meticulous planning to chart the safest route toachieve the desired goals.

The quest for precision in brain surgery is a journey that dates back to the dawn of neurosurgery. Like navigators in uncharted waters, surgeons have constantly explorednew ways to locate and approach intracranial lesions with the utmost accuracy. This quest for precision has led to a continuous development of tools and techniques, eachan evolution of its predecessor, in an effort to map the cerebral terrain with greater clarity.

In the early days of brain surgery, ventriculography stood as a flashlight in the dark, revealing the internal structures of the brain by injecting a contrast medium into the ventricular system. This technique offered a unique view of the cerebral landscape and guided surgeons to lesions near the ventricular cavities, using the deformation they could cause as a reference.

As time went by, surgeons sought more precise and reliable tools, and rigid stereotactic reference frames emerged as beacons lighting the way to surgical precision. These frames, originally designed for animal experimentation, became indispensable allies in human brain surgery because, when placed around the patient's skull and firmly fixed, they provided a system of coordinates that allowed precise localization of intracerebral structures, using reference points on the surface of the skull and places such as the sella turcica and the foramen of Monroe1, revealed thanks to the advance of radiography and ventriculography.

In this odyssey for precision, each tool and technique developed has represented a step forward in the art of brain surgery, bringing surgeons closer to a cure. Hence there are numerous techniques that have been used to increase the extent of brain tumor resection, including neuronavigation, ultrasound and trans-operative magnetic resonance imaging. Justifying the increase in their use even as routine to reduce surgical morbimortality, with higher percentages of total tumor resection, it is therefore necessary to provide surgical alternatives to patients who benefit from these procedures that do not involve higher risk at a lower cost.

The main objective in the management of neoplastic lesions of a neurological nature is complete surgical resection; to this end, with the advent of preoperative imaging through computed tomography (CT) or magnetic resonance imaging (MRI), neurosurgery witnessed an important change, as these became the guidelines for the successful completion of these procedures. In combination with these resources, the use of stereotactic methods helps to achieve greater resection during surgical treatment with the minimum possible neurological complications.

In Mexico, the mortality rate due to malignant tumors represents 10% (89,574) of the total number of reported deaths. Malignant neoplasms of the meninges, brain and

other parts of the central nervous system represent 1.23% of mortality in Mexican men and women aged 0-19 years, and 0.55% in men aged 20-29 years, according to figures updated to 2024 from the National Institute of Statistics and Geography (INEGI). [2]

Through imaging studies based on certain criteria, it is possible to identify neoplasms, necrosis or edema. Neuroimaging allows a differential diagnosis to be made in the early stages to distinguish the tumor from other lesions such as ischemia, infections, pseudotumorous demyelination, among others; it also allows the distinction between a glial tumor and other primary or metastatic tumors to be established. Likewise, by means of these technologies, it is feasible to detect the area of greatest cellular activity, a determining aspect for the degree and extension of the neoplastic lesion; to plan the preoperative strategy, ranging from biopsy to total resection and subsequent radiotherapy; and to follow up the treatment, as well as the progression of the pathology, which includes differentiating a tumor fall from a pseudo-progression or a radionecrosis. [3]

Advances in imaging technology stem from a philosophy of improving brain localization, which aims to make the invisible features of a tumor visible, in order to achieve greater precision and personalization in surgical treatment of the brain. This is why the originator of neurosurgery, Harvey Cushing, stated: "It seems clear that, in order to advance in surgical technique, specialization is required, or better still, concentration of thought and energy in certain directions of work". [4]

It is from these advances in imaging that the search for tools to maximize surgical precision in the resection of brain neoplasms continues to evolve. Proof of this was the introduction of the microscope in the 1970s, [5] as well as other lens and illumination systems, which have improved visibility and precision, making them essential to achieve greater degrees of efficacy and safety.

Now, following this philosophy, another of the objectives to be achieved, beyond just obtaining the best results, is for the interventions to be effective in the shortest possible time, for which the application of other solutions and tools that help to achieve this goal is ideal. The use of sodium fluorescein emerges as an alternative for the visualization of images and signals during the trans-operative period, facilitating rapid decision making during the process.

Sodium fluorescein (FNa) is a fluoropore that has been widely used in the field of ophthalmology. In neurosurgery it has been applied to facilitate the detection of cerebrospinal fluid fistulas via transnasal endoscopy, in cerebral vascular surgery and for resection of brain tumors.

Sodium fluorescein has emerged as a very useful tool in surgical practice, demonstrating its efficacy in various fields, including gynecological and gastrointestinal surgery. It was George Moore and his collaborators who played a pioneering role in the investigation of its application in the neurosurgical field, specifically in the approach to malignant brain tumors, particularly those of glial origin. [6]

The importance of this discovery lies in its contribution to the advancement of neurosurgery, providing surgeons with an additional tool for the accurate identification of tumor lesions during surgical procedures. The findings of Moore and his team laid the foundation for future research in the field of neurosurgery and the clinical application of sodium fluorescein in the treatment of brain tumors.

Since then, the use of sodium fluorescein has been used for the detection of skull base tumor pathology since 2010, with little information. The use of this fluoropore may represent a benefit for further tumor resection with a decrease in morbidity in patients with non-global skull

base tumors. This therapy could be implemented in the future to achieve complete resections, avoiding complications and improving cure rates.

Background

Diagnostic imaging techniques represent an invaluable tool in the detection, evaluation and follow-up of neoplasms. In the context of oncology, these noninvasive modalities have gained a central role, providing detailed information on tumor activity and its response to treatment. From lesion characterization to disease staging, imaging tests play a crucial role in clinical decision making, whether determining the appropriateness of surgery, establishing the parameters for radiotherapy or assessing the need for systemic chemotherapy.

Until November 8, 1895, physicians lacked any means of visually perceiving the inner workings of the human body. It was on this date that Wilhelm Conrad Roentgen accidentally stumbled upon a momentous revelation: the existence of what he called "X- rays" during his experiments with a Crookes cathode ray tube.7 Taking advantage of the absorption principle of X-rays, where bones showed a higher absorption compared to soft tissues and fatty tissue, Roentgen managed to capture clear and distinct images.

In the early 20th century, Alessandro Vallebona, an Italian radiologist, invented conventional tomography based on the simultaneous movement of the X-ray source to keep an object of interest at the center point of the scan plane and defocus all other objects. Although conventional tomography evolved, it remained ineffective for visualization of soft tissues and large areas of the body. Seventy-six years after the birth

of medical imaging, computed tomography (CT) was developed using radiographic projections from multiple angles and then constructing a two-dimensional image with a mathematical model incorporating all the projected data. In 1967, Sir Godfrey Hounsfield invented the first CT scanner at EMI's research laboratories. [7]

Since the invention of the microscope in the 1960s, the efficacy and safety of neurosurgical procedures have been enhanced by image magnification and illumination methods. Likewise, the introduction of image-guided resection such as neuronavigation or intraoperative ultrasound has been facilitating the identification of tumor tissue margins since the 1990s.

Since then, neurosurgery has had important technological advances starting with surgical microscopes, intraoperative ultrasound, brain tomography, magnetic resonance imaging, neuronavigation or neurostimulation, which have represented important advances for the discipline in the last decades.

However, despite advances in illumination and imaging during surgical procedures, intraoperative visualization of brain tumors has remained one of the greatest challenges for neurosurgeons worldwide, especially under white light illumination, where the vast majority of us rely on our experience, making it almost impossible to clearly glimpse the extraction boundaries between the tumor and unaffected areas surrounding the brain tissue.

Sodium Fluorescein

Sodium fluorescein has been well known for different chemical marking techniques for more than 150 years and is still used today in the water industry, for the detection of water or gas leaks as well as in ophthalmic surgery, since in direct contact with water its color turns yellow to green.

During the turn of the century between the 19th and 20th centuries, important discoveries were made in the field of cytology, which was a determining factor in the

development of innovative staining techniques and the synthesis of fluorescents. In the first instance it was Camillo Golgi, who in 1873, initiated the use of silver staining, a technique that was later popularized by Santiago Ramón y Cajal through his detailed neuroanatomical observations. Others followed, such as Paul Mayer in 1896 with hematoxylin and eosin staining, a technique that became fundamental for essential diagnostics; Gustav Giemsa who in 1904 obtained a stain based on eosin and methylene blue that is still in use today for the detection of malaria, among others. [8]

Although dyes provide contrast by modifying the light absorption of cellular structures, fluorescence, with the right equipment, provides superior contrast. However, the

equipment needed to exploit this property has evolved considerably since the first discovery of fluorescence by Nicolas Monardes who, in 1565, documented the remarkable intense blue color of an aqueous extract obtained from wood called "lignum nephriticum"; ninety years later, this same phenomenon was investigated by Athanasius Kircher in Germany, Francis Grimaldi in Italy, as well as Robert Boyle and Isaac Newton in England. In 1845, John Herschel identified the fluorescent properties of quinine sulfate, marking a modern milestone in the study of fluorescence; George Stokes coined the term "fluorescence" in 1852 in his monograph on various fluorescent substances; however, it was not until 1871 that Adolf von Bayer synthesized the first fluorescent dye: fluorescein.8 A year after this breakthrough, Paul Ehrlich used uranine, a sodium salt of fluorescein, to study the secretion of aqueous humor in animal physiology, thus making the first use of this compound as a guide.

At present, the component is characterized as an orange-brown red powder, also known as Uranin A or

Acid Yellow 73, its molecular formula is $C_{20}H_{10}Na_2O_5$, it has a molecular mass of 376.3 g /mole and has a pH of 8.3. It is derived from xanthene dyes, which have a bright coloration ranging in chromatic range from green, yellow to blue, violet.9 It also has an absorption maximum at 494 nm and an emission maximum of 512 nm in water; its main derivatives are fluorescein isothiocyanate (FITC) and, in the synthesis of oligonucleotides, phosphoramidite 6-FAM. [10]

Sodium fluorescein, being particularly soluble, can present two excitation peaks, one between 465 to 490 nm with blue light emission and the other between 510 to 530 nm with green light emission. In combination with water, the reddish-yellow powder immediately turns yellow and under a 560 nm light filter acquires a higher color intensity.

Since its discovery to the present day, this component is widely used by the scientific and medical industry, especially its derivatives Fluorescein isothiocyanate (FITC), Alexa 488 fluorophore.

The basic mechanism of fluorescein is that electromagnetic radiation can excite the electrons of atoms in their basal state to a higher energy state. An energy between 1.5 eV to 3.5 eV is required, which corresponds to light waves between 800 nm and 300 nm.

Fluorescence occurs when electrons relax from their excited state (S1) to their basal state (S0), thus emitting photons. This state of fluorescent radiation that turns into light occurs from picoseconds to nanoseconds.

The fluorescence half-life is the average time the fluoropore remains in the excited state following the excitatory stimulus.

It is this variation in fluoropores that makes their use a tissue contrast possible. The half-life of fluorescein glucuronide, the main metabolite, is 264 minutes and its urinary clearance requires 24 to 32 hours.

Its use in neurosurgery

For many years, researchers have observed and described the differential characteristics of various tissues under ultraviolet light. In 1934, Danckwortt published an extensive monograph covering the entire subject, since then, several authors have described the use of this light as a tool to distinguish neoplastic tissue and some have even claimed specific fluorescence for certain tumors. [11]

It was in October 1946 that George E. Moore reported the first use of sodium fluorescein in patients undergoing laparotomy for gastric carcinoma, in the hope that this substance would accentuate the visual differences between normal and malignant tissues when observed under ultraviolet light. [11]

In 1948, Moore himself published an article in the Journal of Neurosurgery entitled "The Clinical use of Fluorescein in Neurosurgery" in which he highlighted the use of fluorescein in 46 patients diagnosed with brain tumors. In his study, he noted that in only 2 of the patients did the use of fluorescein mark an error or a non-obvious response. Moore and his team concluded that this component proved to be very useful in determining the presence or absence of tumor tissue, in addition to being a good method for confirming the complete removal of infiltrating gliomas. [12]

Also, in his study Moore mentions that because fluorescein is an acid-chromogenic dye, the blood-brain barrier plays an important role in the selectivity of the dye for tumor tissue, and that is because unlike other dyes, such as Evans blue, sodium fluorescein binds to proteins and appears to be an effective low molecular weight marker for brain barrier studies. [13]

After having been used in neurosurgery by George E. Moore, in July 1961, Harold Novotny and David L. Alvis publish the article called method of photographing fluoresence in circulating blood in the human retina in the journal Circulation, describing that injecting FNa into the antecubital vein after 30 seconds illuminates the retinal vessels, it is after this that begins a worldwide acceptance in the application of FNa in ophthalmic surgery as a retinal vessel dye. [16]

Since then, three fluorescent contrasts have been studied and used in neurosurgical procedures in humans: indocyanine green (ICG), 5-aminolevulinic acid (5-ALA) and sodium fluorescein (FNa).

Fluorescein contrasts are classified based on: a) the fluorescent molecule (e.g. intrinsic and extrinsic, endogenous fluoropores) and, b) the excitation/emission wave profile. They can also be divided according to their mechanism of action into:

1. Passive fluorescein (ICG, FNa).
2. Metabolic (5- ALA)
3. Targeted fluorescein.

One of the most important characteristics of these substances is their ability to accumulate in the neoplastic tissue in high concentrations. In addition, they must comply with the following properties: 1) be selective and long-lasting for the tumor tissue, 2) have high fluorescent intensity, 3) do not discolor and 4) do not present systemic effects, toxicity or phototoxicity.

FNa depends on the pH and ionic binding of the solution, so it can be safely administered intravenously in humans, with multiple clinical uses. In addition, it has been reported that the means of distribution of FNa is conjugated with albumin and not alone. [14]

Due to its small molecular size and reversible binding to albumin and red blood cells, sodium fluorescein can extravasate, leading to staining of peritumoral regions. Recently, based on the conjugation of fluorescein to albumin, 5-amino fluorescein- human serum albumin conjugate has been developed and there is a small

clinical trial of 13 patients who have been injected in order to increase the gradient concentration at the tumor/brain interface. [15]

However, years later, in 2003, the publication by Shinoda and collaborators with a series of 105 patients with high-grade glioblastoma, 32 cases were operated with the application of high-dose FNa and with unfiltered microscopy with a total resection of 84.4% in contrast to the 30.1% resection in the non-contrast group. Correlating the areas contrasted with FNa in comparison with those contrasted with gadolinium in magnetic resonance imaging (MRI), thus reaching the conclusion that the areas delimited by the FNa of rupture of the BHH are similar to those observed in T1 sequence in MRI. [17]

These findings were confirmed 5 years later by Koc's group in their series of 80 patients with high-grade glioblastoma including 47 operated on under white xenon light, injected with high doses of 20 mg/kg (FNa), which they then compared with 30 patients who were not injected with the dye. The result was a significant total resection achieved in the first group of 83% versus 55% in the second group. [18]

Another study demonstrating its efficacy at high doses under white xenon light was that of Chen in 2012, who applied intravenous FNa to 10 patients, compared to 12 control patients. The result yielded a difference of 80% total resection observed in the first group versus 33% in the control group, resulting in a significant difference in survival (7.2 months vs. 5.4 months), however, no difference in immediate postoperative neurological status was reported. [19]

For their part, researchers from Kuroiwa's group were pioneers in administering lower doses of FNa 8 mg/kg in a series of 10 patients with high-grade gliomas, using microscopy equipped with Xenon lamps 450 - 490 nm and KODAK Wratten filter no.12 (500 - 530 nm), reporting a total resection of 80% confirmed with cranial tomography and MRI. [20]

In 2013, Roberto Rey - Dios and Aaron Cohen - Gadol were the first to report the use of the Pentero 900 with YELLOW 560 nm filter, specially designed to capture fluoropores in 540 to 690 nm range which they applied to treat 3 cases: brain metastasis, arteriovenous malformation and aneurysm. [21]

The following year, the same Aaron Cohen-Gado together with other specialists in Indianapolis initiated the use of fluorescein in biopsies guided by stereotaxy, administering 3 ml/kg. With a series of 6 patients obtaining 26 samples, calculating a sensitivity and specificity of 79% and 100% respectively. [22]

The first randomized phase 2 study conducted to date for resection of high-grade gliomas in 2011 called FLUOGLIO has begun to yield results regarding the safety in the use of FNa associated with the use of the integrated filter microscope (Pentero Yellow 560, Carl Zeiss Meditec, Germany). Completed with a total of 46 patients that could give a level of evidence 2 - 3 on the efficacy of the use of fluorescein-guided resection in high-grade tumors, the study demonstrated that the use of this technique is safe and reliable in achieving total resections. [23]

Minkin's group presents a series of 11 patients, 5 with low-grade gliomas, 4 patients with tumors of neuroectodermal origin and 2 patients with gangliogliomas. Their study presents a correlation between the degree of fluorophore intensity with the histopathological specimen, finding in all 11 cases trans-surgical and specimen intensity. [24]

In turn, Okuda and collaborators present a prospective analysis of 36 patients with brain metastases with doses of 20 mg /Kg and under xenon white light, reporting total resections in 31 patients. [25] Subsequently, in 2015 that same group reports another series of 30 patients with the aid of the Y560 microscope finding that 90% of the cases presented fluorescence and total resections of

83.3%. [26]

Da Silva and his group prospectively reported 6 patients with skull base tumors (1 vestibular schwannoma, 3 meningiomas, 1 craniopharyngioma and 1 pituitary adenoma) with injections of 1,000 mg of 20% FNa with white xenon light. [27]

In his studies, he mentions that particularly meningiomas present an enhancement of the dural insertion. Subsequently, in 2014, another study was published based on 5 cases with meningiomas of the convexity of the frontal region applying equal doses.28 In August of the same year, the same group published a study of 9 cases of meningiomas of the skull base (1 of the cavernous sinus, 3 petroclival, 1 of the selar tubercle, 2 of the spheroid wing, 1 temporal and one of the olfactory sulcus) where a digital analysis of the contrast between the cranial nerves and the enhancement of the meningiomas was performed, For this study, 1 g of 20% FNa was applied intravenously, also, during the process, photographs were taken under the microscope 10 minutes after applying the FNa, the camera used was Sony DSC-W90 DE 8.1 megapixel. [29]

In 2014 he published another prospective intrasubject study that focused on evaluating the use of sodium fluorescein (SF) in skull base meningioma surgery. Twelve patients with different types of meningiomas located in areas such as the cavernous sinus, olfactory sulcus, petroclival region, tubercle of the sella turcica, sphenoid wings, anterior clinoid and temporal floor participated.

During the surgical procedure, initial dissections were performed and digital images were taken before and after SF injections, using the same light source as the surgical microscope. These images were analyzed using specialized software to calculate SF wavelengths both before and after dye injection.

The results showed significant positive SF enhancement in all types of meningiomas studied, suggesting that this dye effectively highlights tumor areas. Across series, da Silva highlights that SF has key advantages such as low cost, easy availability and safety profile. [30]

On the other hand, the first recorded report of the use of FNa in lymphomas is by Okuda in 2007.31 Höhne in 2016, applies FNa to 7 patients with brain abscesses, establishing the application protocol of 5 ml/kg of weight, intravenous during anesthetic induction (30 to 45 min prior to incision), documented enhancement in the capsule in all 7 cases, with no documented adverse or anaphylactic effects. [32]

Sodium fluorescein provides a strong fluorescence and because of these characteristics it can be observed under white light without requiring a filter; however, integrating a filter allows a more precise delimitation of the tumor borders and requires less dosage. So far its use seems safe because no anaphylactic effects and/or convulsive crises have been described, especially when administered in low doses. With the introduction of microscopes with new filters such as the Pentero 900 with Yellow 560 system (Carl Zeiss) or the FL560 system (Leyla Microsystems), the use of fluorescence has renewed its attention in neurosurgery. [33]

Among the different devices that complement the use of fluorescein in the resection of brain tumors are:

Fluorescein-guided lens devices: a) commercial microscopes with special filters, b) adapting filters to microscopes, c) endoscope and d) non-microscopic fluorescent system. Quantitative fluorescence systems: a) spectroscopy tools, b) laboratory grading system,

c) systems that combine cabinet studies with fluorescein.

3. High resolution endomicroscope.

Commercial microscopes with integrated filters to detect FNa and PpIX date back to 1998.33 These equipment have three components: 1) set of filters for capturing different light waves. b) illumination system

and, c) cameras with special lenses for detection of visible and non-visible light waves (NIR), an example is the Yellow 560 system of the Carl Zeiss company.34 They have achieved with a luminosity set a maximum intensity preserving the necessary illumination (with a spectrum of lower intensity) to identify tissues, with the result of an intensity in the tissue with FNa uptake contrasting with the natural color of the normal tissue in the background.

The Carl Zeiss Meditec YELLOW 560 microscope with an intraoperative fluorescence module has improved image quality by allowing the surgeon to visualize the fluorescence through the objectives and has the advantage of maintaining the natural colors of the surrounding tissues.

This device integrates a 300 watt xenon light source that generates a light in the spectrum close to daylight, however, despite the intensity in wavelength, the temperature remains constant all the time, in addition to this when changing the YELLOW 560 filter the illumination spectrum and the detection of the light wave of the microscope changes, since it is designed to emit a stimulation of 460 to 500 nm and a detection of 540 to 690 nm, emitting a yellowish green color. Thus non-fluorescing tissues appear dimmed when viewed from the microscope screen.

Methodology

The results showed significant positive SF enhancement in all types of meningiomas studied, suggesting that this dye effectively highlights tumor areas. Across series, da Silva highlights that SF has key advantages such as low cost, easy availability and safety profile. [30]

Longitudinal retrospective observational and descriptive. The fluorescence of each tumor was calculated by means of photographs taken with the OPMI pentero 900 Carl Zeiss Meditec YELLOW 560 microscope with an intraoperative fluorescence module, which were projected on a 13-inch MacBook Pro screen Mid 2012, processor 2.5 Ghz intel Core 15, with Intel HD Graphics 4000 1536 MB graphics card with macOS Sierra

operating system using Preview image viewer system version 9.0, which is performed the color calculation using the following technique with resistance system with voltage apparatus and connecting to closed circuit, comparing in both image of the tumor to xenon white light vs tumor under YELLOW 560 filter.

Population

Patients admitted in the period from May to August 2017 with the diagnosis of extrinsic skull base tumors at the National Institute of Neurology and Neurosurgery. Sixteen patients were registered, 12 women (75%) and four men (25%). The age group ranges from 17 to 85 years with a mean of 46.8 years and a median of 50.5 years.

Results

All operated with OPMI pentero 900 Carl Zeiss Meditec YELLOW 560 microscope with an intraoperative fluorescence module, in some cases by hybrid technique, which consisted in performing the approach and part of the resection by trans nasal endoscopic technique (TNE) with transplanum or transclival extension, depending on the case, with support of the fluorescence module by using a trans nasal or trans septal Cushing separator, depending on the type of tumor to be resected.

Tumors are classified according to histology into the following groups: 1) meningiomas, 2) schwannomas, 3) craniopharyngiomas, 4) teratoma, 5) lymphomas, 6) chondrosarcoma and 7) hemangioperitoma.

Of the meningiomas, 3 orbital sphenoidomas were recorded, 2 of the convexity operated by transcranial approach, 1 of the olfactory sulcus using TNE approach

with transplanum extension, giving a total of 6 cases recorded; 4 schwannomas of the pontocerebellar angle resected via transcranial approach with retrosigmoid approach, 2 craniopharyngiomas resected by hybrid technique explained above with transplanum extension, one teratoma of the selar region with transcranial approach using endoport technique and exoscope combined with OPMI pentero 900 Carl Zeiss Meditec YELLOW 560 microscope with an intraoperative fluorescence module, a chondrosarcoma of the clivus with TNE approach and transclival extension, an occipital hemangiopericytoma with transcranial approach and a lymphoma located in the solar region and extension to the sphenoid sinus using the hybrid technique.

There were no cases with anaphylaxis during the administration of sodium fluorescein, in case of side effects described as yellow coloration of the urine, without being able to determine if it is secondary to the means of excretion of the compound determined as choluria, pigmentation of integuments described by yellow pigmentation of mucous membranes, sclerae and skin, or in its case without side effects. As a result (Table 4), one patient presented coloration of the integuments, 9 cases presented choluria, allowing 12 hours after the surgical event, and 6 cases did not present any side effect.

None of those presented persisted for more than 24 hours and no permanent affectation to any organ was registered according to laboratory studies. Fluorescence of the tumors was recorded in all cases, however, no clear distinction was observed on direct vision under the microscope with respect to the lesions in case of schwannomas with cranial nerves and in case of spheno-orbital meningiomas with the boundary with non-infiltrated bone.

This was quantified with a voltmeter designing the ends to determine the resistance emitted from photoluminescence observed in the images taken with the microscope, projected on the screen of the computer with which the present work is performed (MacBook Pro with a processor 2.5 GHz Intel Core i5 processor and an Intel HD Graphics 4000 1536 MB graphics card) through an electronic system based on a motion detector circuit, where any brightness level triggers the two optical sensors (photo resistors), which detect the light levels under a contrast. So when the input of the light emitting diode (LED: light emitting diode) is registered, a change (pulse) is triggered and the output is sent to the monostable oscillator, this is due to the response or the difference between the optoelectronic sensors is very fast, which is recorded in Ohms that measures the emitted resistance with results for the images under the microscope with white xenon light and under the YELLOW 560 filter, which under non- parametric statistical test of independent variables gives a significance of 0.05.

Discussion

At present, there are no standard protocols for the application of fluorescein in Mexico, having the convenient use of the microscope with adapted filter that grants the possibility of obtaining similar results at lower doses applied and as a result the decrease in the appearance of side effects, without describing anaphylactic reactions at the moment in any study.

That is why we undertook its use without any standard, performing our own protocol, where the patients, once the diagnosis was made and it was determined that they required surgical management, were prepared with the standardized institutional protocol that is given to any patient who will undergo a surgical procedure, once in the operating room and under the effects of balanced general anesthesia and with monitoring by the anesthesia service, doses of 8 mg/kg were administered at a concentration of 10% being the presentation of the 5 ml ampoules at a dose of 100 mg/ml; in the case of the 20% concentration presentation, an adjustment was made to maintain the mentioned dose.

Administering the fluoropore at the beginning of the surgical event (during the incision) that for the different types of approaches performed, described in the results it is not possible to obtain an average duration of the approach, observing however in all cases fluorescence at the time of identifying the lesion, one of the primary objectives in the study was to demonstrate the same results obtained by the Da Silva group where they describe the clear distinction between lesion and cranial nerves and neuronal tissue to improve the rate of resection, in the case of schwannomas however this is not observed during our cranial procedures with respect to the tumor and likewise we do not justify its use in meningiomas proper to the base of the skull such as those originating in the sphenoorbital region since the distinction is not clear under the filter of the lesion with respect to non- infiltrated bone, In the case of the dural tail in the meningiomas of the convexity, an important enhancement is observed, however this is identified under white xenon light, however it is demonstrated by means of the images and the use of the voltmeter that there is a clear fluorescence of all the tumors independently of the histopathological lineage.

The application and dosage has been found to vary in different studies, nor has it been identified with other factors such as extravasation in the intervened tissue, cerebral edema or distribution patterns. The simultaneous application of 5-ALA has shown that fluorescein is observed in normal tissue and that it is not detected by the metabolite PpIX, which is why the resection of malignant lesions remains in doubt. Some researchers have even commented that the use of fluorescein in this field is very premature due to the false positives and negatives that can occur during surgery. Not all metastases or tumors of primary origin in the central nervous system are susceptible to the use of fluorescein and likewise no studies have been done where residual tissue that did not enhance FNa correlates with MRI.

Other considerations are the low cost of acquiring the molecule, which is now an imminent consideration for obtaining medical care worldwide. It is important to emphasize that the study group is small and above all limits the statistical study since they are different histopathological strains, which may be the reason why the results obtained by other groups are not observed. In the same way, a greater extension of the same is considered in the future to digitally demonstrate this difference by means of computer programs that allow the measurement by pixels of greater precision.

This is the first study to be carried out in Mexico and, in comparison with other series, it has a significant number of patients reported despite the fact that they are different types of tumors.

The use of other equipment such as the endoscope has been initiated with filters already adapted to be able to carry out the growths without the need to do it in a hybrid way as it had to be done at the time of the study. Leaving to the expectation if other results could be reported and with it another utility in this field.

References

1. Chorreno Parra, J. A; Carnalla Cortés, M; Flores Vázquez J. C; Ruíz Rivero, C.O; Guadarrama Ortíz, P. Neuronavigation: image-guided neurosurgery [internet]. 2018. [Accessed February 14, 2024]; 19(4): 83-93. Available from: https://www.medigraphic.com/pdfs/revmexneu/rmn-2018/rmn184i.pdf
2. National Institute of Statistics and Geography [Internet]. Mexico: National Institute of Statistics and Geography. Release number 78/24. February 4, 2024 [accessed February 14, 2024]. Available at: https://www.inegi.org.mx/contenidos/saladeprensa/aproposito/2024/EAP_CANCER2 4.pdf
3. Halfon, Mario Javier; Báez Alejandra; Casas

Parera Ignacio; Báez, Mariana; Blumenkrantz, Yamila; et al. Neurology Arg [Internet]. 2013 [Accessed February 14, 2024]; 5(1): 37 (6). Available at: https://www.elsevier.es/es-revista-neurologia- argentina- 301-pdf-S1853002812001139

4. YASARGIL MG. Microsurgery. Applied to Neurosurgery. Georg Thieme Verlag. 1969. XV-XVI: 1 (2).
5. Benedek, P., and Stable M. The operating microscope in neurosurgery. Crn. Uruguay. 1977; 47 (2): 141 (2).
6. Reyes Gasga J, Reyes Gasga J. Brief historical review of electron microscopy in Mexico and the world. Mundo nano Interdisciplinary journal in nanosciences and nanotechnology[Internet]. 2020 Sep1;13(25):79-100. Available in: http://www.scielo.org.mx/scielo.php?pid=S2448- 56912020000200079&script=sci_arttext
7. Moore, G. E. Fluorescein as an Agent in the Differentiation of Normal and Malignant Tissues. Science [internet]. 1943. [Accessed February 14, 2024] (106) 2745:130-131. Available at: https://www.science.org/doi/abs/10.1126/science.106.2745.130.b
8. Bercovich E, Javitt MC. Medical Imaging: From Roentgen to the Digital Revolution, and Beyond. Rambam Maimonides Med J. [Internet] 2018 [Accessed February 17, 2024] 4;9(4):e0034. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6186003/
9. Heinrichs A. Stains and fluorescent dyes. Nature Cell Biology. 2009 Oct;11(S1):S7- Available at: https://www.nature.com/articles/milelight02
10. Mauro J., Agudelo L. Degradation of sodium fluorescein by heterogeneous photocatalysis in a heliophotocatalytic reactor. Technological University of Pereira, Technological Faculty, School of Chemistry, Pereira Chemical Technology Program [Internet]. [cited 2024 Sep 12]. Available at: https://repositorio.utp.edu.co/server/api/core/bitstreams/0ed225a1-19e7- 40b0-8ca1-2f54e066796e/content ww.instijlmedia.nl.
11. Fluorescein sodium salt (C.I.45350) [Internet]. Laboratorium Discounter.2024 [cited 2024 Sep 12]. Available from: https://www.laboratoriumdiscounter.nl/es/quimicos/a-z/f/sal-de-fluoresceina-sodica-ci-45350/.
12. Mooíe GE. Fluoíescein as an Agent in the Diffeíentiation of Noímal and Malignant l'issues. Science. 1947;106(2745):130-131. doi:10.1126/science.106.2745.130-a. Available at: https://pubmed.ncbi.nlm.nih.gov/17750790/.
13. Moore, G. E., Peyton, W. T., French, L. A., & Walker, W. W. (1948). The Clinical Use of Fluorescein in Neurosurgery. Journal of Neurosurgery, 5(4), 392-398. doi:10.3171/jns.1948.5.4.0392. Available at: https://thejns.org/view/journals/j-neurosurg/5/4/article-p392.xml.
14. Saunders NR, Dziegielewska KM, Møllgård K, Habgood MD. Markers for blood- brain barrier integrity: how appropriate is Evans blue in the twenty-first century and what are the alternatives? Frontiers in Neuroscience. 2015 Oct 29;9. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624851/
15. Ficha Técnica [Internet]. Available at: https://cima.aemps.es/cima/pdfs/es/ft/65458/65458_ft.pdf
16. Ding R, Frei E, Mahmoudreza Fardanesh, Schrenk HH, Kremer P, Haefeli WE. Pharmacokinetics of 5-Aminofluorescein-Albumin, a Novel Fluorescence Marker of Brain Tumors During Surgery. The Journal of Clinical Pharmacology [Internet]. 2011 May 1

[cited 2024Sep12];51(5): 672-8.
Available from:
https://pubmed.ncbi.nlm.nih.gov/20978277/

17. Novotny HR, Alvis DL. A Method of Photographing Fluorescence in Circulating Blood in the Human Retina. Circulation. 1961 Jul;24(1):82-6. Available at: https://pubmed.ncbi.nlm.nih.gov/13729802/
18. Shinoda J, Yano H, Yoshimura SI, Okumura A, Kaku Y, Iwama T, et al. Fluorescence-guided resection of glioblastoma multiforme by using high-dose fluorescein sodium. Journal of Neurosurgery. 2003 Sep;99(3):597-603. Available at:
https://pubmed.ncbi.nlm.nih.gov/12959452/
19. Koc K, Anik I, Cabuk B, Ceylan S. Fluorescein sodium-guided surgery in glioblastoma multiforme: a prospective evaluation. British Journal of Neurosurgery. 2008 Jan;22(1): 99-103. Available at: https://pubmed.ncbi.nlm.nih.gov/18224529/.
20. Chen B, Wang H, Ge P, Zhao J, Li W, Gu H, et al. Gross Total Resection of Glioma with the Intraoperative Fluorescence-guidance of Fluorescein Sodium. International Journal of Medical Sciences [Internet]. 2012 Oct 6 [cited 2020 Oct 25];9(8): 708-14. Available from:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3477680/
21. Kuroiwa T, Yoshinaga Kajimoto, Ohta T. Development of a Fluorescein Operative Microscope for use During Malignant Glioma Surgery. Surgical Neurology. 1998 Jul 1;50(1): 41-9.
Available at:
https://pubmed.ncbi.nlm.nih.gov/9657492/
22. Rey-Dios R, Cohen-Gadol AA. Technical principles and neurosurgical applications of fluorescein fluorescence using a microscope-integrated fluorescence module. Acta Neurochirurgica. 2013 Feb 8;155(4):701-6. Available at:
https://pubmed.ncbi.nlm.nih.gov/23392589/
23. Li YP, Rey-Dios R, Roberts DD, Valdes PA, Cohen-Gadol AA. Intraoperative Fluorescence-Guided Resection of High-Grade Gliomas: A Comparison of the Present Techniques and Evolution of Future Strategies. World Neurosurgery. 2014 Jul 1;82(1- 2):175-85. Available at:
https://pubmed.ncbi.nlm.nih.gov/23851210/
24. Acerbi F, Broggi M, Schebesch KM, Höhne J, Cavallo C, De Laurentis C, et al. Fluorescein-Guided Surgery for Resection of High-Grade Gliomas: A Multicentric Prospective Phase II Study (FLUOGLIO). Clinical Cancer Research [Internet]. 2018 Jan 1 [cited 2023 Jan 30]; 24(1):52-61. Available from:
https://aacrjournals.org/clincancerres/article/24/1/52/15206/Fluorescein-Guided- Surgery-for-Resection-of-High
25. Minkin K, Naydenov E, Gabrovski K, Dimova P, Penkov M, Tanova R, et al. Intraoperative fluorescein staining for benign brain tumors. Clinical Neurology and Neurosurgery. 2016 Oct;149: 22-6. Available at:
https://www.sciencedirect.com/science/article/abs/pii/S0303846716302554
26. Okuda T, Kataoka K, Tomonari Yabuuchi, Haruki Yugami, Kato A. Fluorescence- guided surgery of metastatic brain tumors using fluorescein sodium. 2010 Jan 1;17(1):118-21. Available at:
https://pubmed.ncbi.nlm.nih.gov/19969462/
27. Okuda T, Yoshioka H, Kato A. Fluorescence-guided surgery for glioblastoma multiforme using high-dose fluorescein sodium with excitation and barrier filters. Journal of Clinical Neuroscience. 2012 Dec;19(12):1719-22. Available at:
https://pubmed.ncbi.nlm.nih.gov/23036170/
28. da Silva C, da Silva JB, da Silva V. Use of

29. sodium fluorescein in skull base tumors. Surgical Neurology International. 2010; 1(1):70. Available at: https://pubmed.ncbi.nlm.nih.gov/21125008/
30. da Silva C, da Silva V, da Silva JL. Convexity meningiomas enhanced by sodium fluorescein. Surgical Neurology International. 2014; 5(1):3. Available at: https://pubmed.ncbi.nlm.nih.gov/24575318/
31. da Silva V, da Silva J, da Silva C. Skull Base Meningiomas and Cranial Nerves Contrast Using Sodium Fluorescein: A New Application of an Old Tool. Journal of Neurological Surgery Part B: Skull Base. 2014 Apr 17; 75(04):255-60. Available at: https://pubmed.ncbi.nlm.nih.gov/27054056/
32. da Silva CE, da Silva VD, da Silva JLB. Sodium fluoíescein in skull base meningiomas: A technical note. Clinical Neuíology and Neuíosuígeíy. 2014 May;120:32-5. Available at: https://pubmed.ncbi.nlm.nih.gov/24731572/
33. Okuda. T. Effectiveness of intraoperative fluorescence for diagnosis of malignant lymphoma. Neurological surgery [Internet]. 2023 [cited 2024 Sep 12];36(11). Available from: https://pubmed.ncbi.nlm.nih.gov/19048918/
34. Höhne J, Brawanski A, Karl-Michael Schebesch. Fluorescence-guided surgery of brain abscesses. Clinical Neurology and Neurosurgery [Internet]. 2017 Apr 1 [cited 2024 Sep 12]; 155:36-9. Available from: https://pubmed.ncbi.nlm.nih.gov/28242559/
35. Uluç K, Kujoth GC, Başkaya MK. Operating microscopes: past, present, and future. Neurosurgical Focus. 2009 Sep;27(3): E4. Available at: https://pubmed.ncbi.nlm.nih.gov/19722819/.
36. Kriss TC, Kriss VM. History of the Operating Microscope: From Magnifying Glass to Microneurosurgery. Neurosurgery. 1998 Apr 1;42(4):899-907. Available at: https://pubmed.ncbi.nlm.nih.gov/9574655/