ABSTRACT

Since hypertension raises the risk of cardiovascular disease and other consequences, it must be considered when deciding on a patient’s course of treatment. Hypertension is the most dangerous adverse effect of corticosteroid use. Corticosteroid treatments, generally known as steroids or anti-inflammatory pharmaceuticals, are used to treat a variety of diseases. They differ from anabolic steroids, which some people often use illicitly to gain muscular mass. Despite being essential in the care of many inflammatory and immunologic illnesses, systemic corticosteroids carry a number of hazards. Osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, Gushing’s syndrome, psychiatric disorders, and immunosuppression are some of the more severe adverse effects of systemic corticosteroid therapy, particularly when taken in high dosages for lengthy periods of time. Using the most recent data as well as the authors’ clinical expertise, this extensive study discusses these adverse occurrences and offers helpful advice for their prevention and management.

Keywords: Hypertension, Steroid, Hazard effects, Aldosterone, Prednisone, Dexamethasone

INTRODUCTION

Blood pressure is the amount of force that is exerted on the arterial walls by blood as it is pumped around the body by the heart. High blood pressure (hypertension) occurs when blood is pumping with more force than normal through arteries. Corticosteroids have been one of the most frequently used therapeutics in ophthalmology over the past decades, known for their potent anti-inflammatory and immunosuppressive action [1]. Intraocular pressure (IOP) elevation has proven to be a significant ocular side effect that could accompany steroid use. Different mechanisms of IOP rise due to corticosteroid use have been postulated. The ocular-hypertensive corticosteroid response has been well-documented in adults. Conversely, there are very few studies describing the ocular side effects of corticosteroids in the pediatric age group, and to the best of our knowledge, none of them included children of North African descent. This might be attributed to the technical difficulty to measure the IOP in children.

The principal mechanism of corticosteroid-induced hypertension is the overstimulation of the mineralocorticoid receptor, resulting in sodium retention in the kidney. This results in volume expansion and a subsequent increase in blood pressure. Corticosteroid-induced hypertension may respond to diuretic therapy. Corticosteroids have been one of the most frequently used therapeutics in ophthalmology over the past decades, known for their potent anti-inflammatory and immunosuppressive actions [1]. Intraocular pressure (IOP) elevation has proven to be a significant ocular side effect that could accompany steroid use. Different mechanisms of IOP rise due to corticosteroid use have been postulated. The ocular-hypertensive corticosteroid response has been well-documented in adults. Conversely, there are very few studies describing the ocular side effects of corticosteroids in the pediatric age group, and to the best of our knowledge, none of them included children of North African descent. This might be attributed to the technical difficulty to measure the IOP in children [2].

Increased intraocular pressure (IOP) can occur as a consequence of oral, intravenous, inhaled, topical, periocular, or intravitreal corticosteroid therapy. If the ocular hypertension is of a significant magnitude, not recognized, and not treated, subsequent glaucomatous optic neuropathy can develop (that is, steroid-induced glaucoma). Steroid-induced ocular hypertension was first reported in 1950 when McLean reported an increase in IOP associated with the systemic administration of adrenocorticotropic hormone (ACTH). The first report of increased IOP caused by the local administration of cortisone occurred four years later [3]. Since those initial reports, corticosteroid-induced glaucoma has been studied intensively. A number of predisposing. The intraocular potency and mode of administration have been shown to be important in initiating an ocular hypertensive response. Recently, the popular use of intravitreal triamcinolone acetonide (IVTA) for subretinal fluid, macular edema, and adjunctive therapy in the treatment of choroidal neovascularization has led to an increased incidence of corticosteroid-induced ocular hypertension from IVTA. The molecular biological factors contributing to increase IOP are beginning to be better understood, and these findings may lead to additional management options in the future. We will review selected studies with an emphasis on glaucoma elevations associated with IVTA [4]. Predisposing risk factors for corticosteroid-induced glaucoma when treated with topical steroids for 4–6 weeks, 5% of the population demonstrates a rise in IOP greater than 16 mmHg and 30% have a rise of 6–15 mmHg. Several variables have been identified as predisposing risk factors for steroid-induced ocular hypertension. Patients with predisposing risk factors should be followed more diligently when receiving corticosteroids. Primary open-angle glaucoma (POAG) patients and glaucoma suspects were shown to be at an increased risk for elevated IOP after treatment with corticosteroids. Studies by Armaly revealed that approximately one-third of glaucoma suspects and more than 90% of POAG patients responded with an IOP elevation greater than 6 mmHg after receiving a 4-week course of topical dexamethasone 0.1%. The effect was noted to be more prominent in the eyes of older adult patients compared with the eyes of younger patients. A study by Becker and Mills also indicated that patients with preexisting glaucoma and glaucoma suspects demonstrated large, highly significant increases in IOP in 2–4 weeks with the use of topical betamethasone 0.1% and exhibited decreased outflow facility during the treatment period. The IOP returned to baseline or normal in approximately 1 week with discontinuation of steroid treatment. Moreover, other studies showed that simply having a first-degree relative with POAG could make one susceptible to being a steroid responder [5]. Although older patients are at increased risk, the frequency of steroid responsiveness with age may occur in a bimodal distribution. Children as a group have been...
shown to be greater steroid-responders as compared with adults. A recent study by Lam et al. showed that 71.2 and 59.2% of children receiving topical dexamethasone 0.1% (four times per day and two times per day, respectively) responded with an IOP rise greater than 21 mmHg. Additionally, 36.4 and 21.1% of those same two groups had an IOP rise greater than 30 mmHg. Among children under 6 yr old who received dexamethasone 0.1% four times per day, the peak IOP was greater, the net increase in IOP was greater, and the time required to obtain the peak IOP was less. Children greater than 6 yr old (children up to age 10 were included in the study) had a similar net increase in IOP, but did not show a significant difference in peak IOP or the time required to reach the peak IOP [6]. Corticosteroid-induced ocular hypertension associated with triamcinolone acetonide IVTA has become a useful therapy for many conditions, including uveitis, veno-occlusive disease, diabetes, and choroidal neovascularization. When given intravenously, triamcinolone acetonide is 35 times more potent as an anti-inflammatory agent than cortisol. As the list of indications and use of IVTA increases, the incidence of corticosteroid-induced glaucoma associated with IVTA will be more common and more likely to be encountered by ophthalmologists. In a recent meta-analysis, Jonas found that intravitreal dosages of approximately 20 mg (the dose more commonly used in Europe) are associated with a 41% prevalence of an IOP elevation greater than 21 mmHg. All but one patient was managed with topical glaucoma medications and medications were no longer needed about 6 mo after the injection. The one patient that required surgery underwent trabeculectomy 9 mo after injection and fluid aspirations obtained during surgery contained soluble triamcinolone. It was concluded that IVTA may last 9 mo or longer and this fact should be considered prior to repeating the injection.

Optical ophthalmic drops/ointments

These are still the most common methods of administering steroids to the eye and following a significant steroid response in a human aqueous humour within 15-30 min 3132. Not surprisingly, increased steroid concentration in topical preparations generally results in higher intraocular concentrations,3 14 but for prednisolone acetate the optimum dose-response effect in experimental keratitis occurs at a 1% concentration and is not improved by further increases in concentration.20 Increasing ocular contact time by preparing topical steroids in a micro-suspension,25 gel, or viscous formulation556 can double the corneal and aqueous humour concentrations of steroid compared with the same drug applied as a solution.33556 Other apparently minor changes in formulation, such as the addition of benzalkonium, can significantly alter the pharmacokinetics of topical steroids.3 For these reasons, many ophthalmologists prefer to use commercially prepared ‘off-the-shelf’ preparations rather than attempt to modify the formulation in an attempt to unravel differences in pharmacokinetic behavior, which may be associated with clinical efficacy [7].

Prevention of Adverse drug reactions

There are two fundamental methods that can be used to do so: 1) Determine the subgroup of patients who are most likely to experience the negative effect and change the recommended course of treatment accordingly. 2) Make sure any potential negative effects are minimized in the treatment plan11 [8].

Identifying susceptibility

Knowledge of patient susceptibilities can inform your prescribing decision and reduce the risk of an ADR. A patient’s medication history will identify any previous ADRs and, therefore, preclude re-exposure to the drug. In other cases, susceptibility factors such as age, gender, pregnancy status and ethnicity can help predict the risk of an ADR occurring. Pharmacokinetics is starting to yield more personalized medicine choices by predicting who is more susceptible to suffer a specific ADR12 [9].

Reporting adverse drug reaction

An efficient pharmacovigilance (PV) system is required to monitor the safe use of medication in order to promote public health. PV is characterized as the science and endeavors concerned with the identification, evaluation, comprehension, and avoidance of unfavorable consequences or any other potential drug-related issues.

Procedures for reporting

Obtain patient history and do a proper examination: Take a proper history. A full medical history should be done properly. Can an ADR be explained by other causes e.g. patient’s underlying disease, other prescription medicine/s, OTC medicines or complementary medicines, toxins or foods. It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is. A medicine-related cause should be considered, especially when other causes are not contributing to the patient’s medical condition. 23 Where necessary, do a thorough physical examination with appropriate laboratory, imaging and other relevant investigations [10]. Few medicines produce distinctive physical signs (exceptions include fixed drug eruptions, steroid-induced dermal atrophy, acute extrapyramidal reactions). Laboratory tests are especially important if the medicine is considered essential in improving patient care or if the laboratory test results will improve management of the patient. Try to describe the reaction as clearly as possible and where possible provide an accurate diagnosis or pictures [11]. For the Indian Pharmacovigilance Program, the Indian Pharmacopoeia Commission (IPC), Ghaziabad, serves as the National Coordination Center (NCC) (PvPI). At order to track and gather ADR reports under NCC-PvPI, 150 ADR monitoring centers (AMCs) were set up in various hospitals and medical facilities throughout India. Regardless of whether there is a proven causal connection between a drug and the reaction, PvPI supports the reporting of all suspected ADRs, regardless of whether they are known, unknown, serious, non-serious, common, or rare24. It is possible to record ADRs associated with the use of contrast media, vaccinations, conventional drugs, medical equipment, etc. ADRs can be reported to NCC or AMCs by all healthcare providers (doctors, dentists, pharmacists, nurses), as well as patients and consumers. Additionally, pharmaceutical firms have the option of sending NCC-specific case safety data for their product 25. On the IPC website, forms for reporting suspected ADR are available for consumers and healthcare practitioners. The consumer reporting form is made available in 10 regional languages in order to eliminate linguistic barriers in ADR reporting (Hindi, Tamil, Telugu, Kannada, Bengali, Gujarati, Assamese, Marathi, Oriya, and Malayalam) [11, 12].

Hypertension

When the diastolic blood pressure is higher than 90 mm Hg and the systolic blood pressure is higher than 140 mm Hg, the condition is known as hypertension29. It is a chronic condition that is regarded as one of the most serious public health problems and a major cardiovascular risk factor. The World Health Organization (WHO) estimates that elevated blood pressure causes at least 7.1 million deaths annually. One of the main factors contributing to early morbidity and mortality worldwide is high blood pressure30. The Non-Communicable Diseases (NCD) Risk Factor Collaboration (NCD-RFCD) risk factor analysis shows that the number of patients with arterial hypertension is steadily rising, doubling between 1990 and 2019 to reach over 1.2 billion people. By 2025, 1.5 billion people will have hypertension, according to data projections31 [13]. Despite the prosperity of a particular nation, there remains a significant prevalence of arterial hypertension recorded globally. Rarely does hypertension develop as a standalone illness. It frequently coexists with additional cardiovascular disease risk factors, such as type 2 diabetes, hypercholesterolemia, gout, or obesity, as well as clinically obvious cardiovascular system complications, like ischemic heart disease, heart failure (HF), and atrial fibrillation (AF), which adds to the therapeutic challenge [14].

A novel approach to treating patients with resistant hypertension using radiofrequency ablation (RFA) of renal sympathetic nerves was recently reported. The rationale for this approach is that renal sympathetic tone plays a role in the pathogenesis of resistant hypertension. The RFA was used to destroy renal sympathetic nerves using radiofrequency ablation (RFA) of renal sympathetic nerves...
Hypertension is a common medical condition that affects many people (high blood pressure). High blood pressure may have come up frequently in conversation with our friends and family. It might appear to be a common medical issue that is safe. Hypertension has a significant impact on cardiovascular disease. Adults with hypertension make up almost one-third of those who are currently undiagnosed, and of those who are, about half do not take antihypertensive medications. The World Health Organization (WHO) has estimated that high blood pressure kills at least 9 million people annually, either directly or indirectly. As a prevalent preventable cause of cardiovascular disease and mortality, hypertension has a significant negative impact on older people’s independence and quality of life. The quality of life and independence of older people can be greatly affected by hypertension, a common preventable cause of cardiovascular morbidity and death. The fact that you might not experience any symptoms until your hypertension is severe is one of its most dangerous aspects. Most people with hypertension don’t exhibit any symptoms. As a result, hypertension is referred to as the “silent killer.” The sum of systemic vascular resistance and cardiac output is used to calculate blood pressure. A rise in either cardiac output or systemic vascular resistance, or even both, may be observed in people with arterial hypertension as a result. Cardiovascular output is frequently increased in younger patients, but in the elderly, vasculature stiffness and rising systemic vascular resistance play a major role [3]. Blood pressure is the amount of pressure that your body’s blood exerts against the walls of your arteries and other significant blood vessels. Blood pressure is determined by two means:

- Systolic blood pressure: It is the amount of pressure in your arteries when the heart beats.
- Diastolic blood pressure: It is the amount of pressure in your arteries between heartbeats.

Blood pressure readings are expressed as two numbers and are expressed in millimeters of mercury (mm Hg). The first number denotes systolic pressure, while the second number denotes diastolic pressure. The first number denotes systolic pressure, while the second number denotes diastolic pressure. When your blood pressure readings are higher than usual, you have hypertension. A blood pressure reading of 140/90 mm Hg or higher is generally regarded as hypertension.

Methodology

A total of 40 patients (80 eyes) undergoing bilateral recession strabismus surgery were divided into two groups. Group A included 20 children (40 eyes); for each, one eye was randomized to receive 1% Rimexolone and the fellow eye received 0.1% Dexamethasone. Group B included 20 children (40 eyes); for each, one eye was randomized to receive 1% Rimexolone and the fellow eye received 0.1% Fluorometholone. Patients received eye drops for two consecutive weeks. Preoperative and postoperative intraocular pressure values were measured [16]. We conducted a randomized contralateral comparative clinical trial that was performed on 80 eyes of 40 children under 13 y of age undergoing bilateral symmetric strabismus recession surgery in Cairo University Hospitals (Cairo University Specialized Pediatric Hospital–Abu Al Reesh and Kasr Al Ainy Hospital) from the period between October 2015 and April 2016. An estimation of sample size was performed considering a study power of at least 0.8 with an alpha error of 0.05, aiming to detect a difference of 4 mmHg in mean IOP in the postoperative week 6 between the two groups, assuming a standard observation. These BP reductions are similar to those observed in the therapeutic studies of resistant hypertension reviewed last year. These initial studies of RFA of the renal nerves seem to justify this novel approach to treatment, but further large-scale studies are required to determine the place of this approach in more routine clinical practice [15].
deviation (SD) of 4 mmHg. On the basis of this estimation, a total of 17 eyes in each group were found to be adequate, and considering a total of 20% dropout during the follow-up, recruitment of at least 20 study subjects in each group was targeted. The study was approved by the local Institutional Review Board in our institution, and a parent/guardian informed consent was obtained for all children [17]. The laboratory findings were: hematocrit, 48.4%; erythrocyte sedimentation rate, 31 mm/hr; positive Rose Waaler and latex tests; negative DNA binding; plasma sodium, 135 mmol/liter; potassium, 5.9 mmol/liter; chloride, 98 mmol/liter; bicarbonate, 27 mmol/liter; creatinine, 0.08 mol/liter (0.9 mg/dl); urate, 0.31 mmol/liter (5.2 mg/dl); albumin, 35 g/liter (3.5 g/dl); and fasting blood glucose, 5.7 mmol/liter (103 mg/dl). Full blood examination (hemoglobin, differential white cell, and platelet count), liver function tests, serum lipids, electrocardiogram, chest x-ray, and urine microscopy all were normal. Plasma renin concentration was 20 dU/ml (normal ambulant range, 11—75. dU/ml). The steroid therapy was reduced gradually. His symptoms of arthritis flared but were controlled with naproxen suppositories, and administration of intramuscular gold was commenced. Immunosuppressive therapy was considered for the epidermis but was withheld while the disease remained controlled. He currently takes 15 mg of prednisolone daily. Glibenclamide has been withdrawn [18]. The study included children younger than 13 y of age who underwent bilateral symmetrical strabismus recession surgery and had a preoperative IOP of 21.00 mmHg or less, with a cup-disc ratio of 0.3 or less. The study excluded children who could not comply with the IOP measurements with no sedation or anesthesia other than topical anesthesia or children who had a family history of glaucoma or high myopia in the first-degree relatives. Children who had a systemic or ocular disease (apart from strabismus) or had a history of previous steroid usage were also excluded from the study [18].

Animals

All animal experiments were performed according to the Association for Research in Vision and Ophthalmology (ARVO) guidelines. Twelve healthy (female) cows between 3 and 5 y of age and weighing 350 to 420 kg were selected from a local ranch in Corrientes, Argentina, for the corticosteroid study. They were of a common type in Argentina named Braford, a cross between Brahman and Hereford. Two of the cows were pregnant, and 1 lost the fetus during the study because of unrelated reasons, without affecting the health of the mother. The cows were tagged for the fetus during the study because of unrelated reasons, without affecting the health of the mother. The cows were tagged for

Measurement of IOP

With the handheld Perkins application tonometer once the cow was held in the yoke and a cowboy moved the cow’s head to a proper orientation, the ophthalmologist measured the IOP with the Perkins tonometer. Before the IOP measurement, 2 drops of topical 0.5% proparacaine (Alcon Argentina) followed by 2 drops of 0.25% fluorescein were instilled. Two sets of measurements were taken on each eye, alternating first one eye and then the other. The ophthalmologist measuring the IOP was unaware of the treatment of each eye [23].

All IOP measurement

The study will be conducted in the NIMS Hospital, Jaipur, Raj (India), from the month of September 2022 up to the month of December 2022. In this study, the targeted patient will be classified according to their medication pattern. The patient data will be collected in the CRF form. To study the mechanism of corticosteroid-induced ocular hypertension is increased aqueous outflow resistance. There are a number of observations that can be simplified into three broad categories: corticosteroids can induce physical and mechanical changes in the microstructure of the trabecular meshwork; cause an increase in the deposition of substances in the trabecular meshwork, thereby causing decreased outflow facility; and inhibit proteases and trabecular meshwork endothelial cell phagocytosis causing a decrease in the breakdown of substances in the trabecular meshwork [24].

The pathophysiology of corticosteroid-induced ocular hypertension and glaucoma

The mechanism of corticosteroid-induced ocular hypertension is increased aqueous outflow resistance. There are a number of observations that can be simplified into three broad categories: corticosteroids can induce physical and mechanical changes in the microstructure of the trabecular meshwork; cause an increase in the deposition of substances in the trabecular meshwork, thereby causing decreased outflow facility; and inhibit proteases and trabecular meshwork endothelial cell phagocytosis causing a decrease in the breakdown of substances in the trabecular meshwork may cause a decrease in outflow facility and an increase in IOP. Clark and colleagues [24] showed that the actin stress fibers were reorganized into actin networks that resembled geodesic-dome-like polygonal lattices in human trabecular meshwork cells cultured in the presence of dexamethasone. Upon discontinuing dexamethasone, cross-linking of the actin networks was reversible. The effect was thought to be mediated via trabecular meshwork glucocorticoid receptors [25, 26]. Corticosteroids also increase the deposition of ECM in the trabecular meshwork, leading to decreased outflow facility. A study by Wilson et al. [27] found an increased deposition of ECM material, altering the ultrastructure of the juxtanaculcular region. The corticosteroid dexamethasone increases glycosaminoglycan, elastin, and fibronectin production in cultured trabecular meshwork; the glycosaminoglycan deposition increases further with prolonged steroid exposure [27, 28]. Myocilin is a 55 kDa protein that has also been shown to be induced in cultured human trabecular meshwork cells after exposure to dexamethasone for 2–3 w [29]. Mutations in myocilin have been shown to be associated with juvenile-onset and adult-onset POAG. Controversy exists as to if myocilin causes an increase or a decrease in the outflow facility. In studies of perfused human trabecular meshwork cell cultures, recombinant myocilin decreased outflow facility, while studies of viral-mediated transfer of myocilin in trabecular meshwork cells caused overexpression of myocilin and increased outflow facility [30].

Discussion of study

Our study showed that Dexamethasone resulted in a more severe elevation of IOP than Rimexolone and Flurometholone, whereas...
Fluorometholone and Rimexolone showed comparable effects on the rise of IOP. In our study, corticosteroid use was stopped after 2 w. The rise in IOP was transient. In the sixth week of follow-up, although not clinically significant, the mean this research is oriented to evaluate the common hazards of steroids in general patients also to observe the co-morbidity. The study is designed for public awareness by which we can prohibit the bizarre outcome caused by the misuse of drug, it will also evaluate the prescribing factor in general patients about medication. In this study will target a particular category of patients suffering from hypertension by questioning them regarding to their health concern and medication pattern. We conducted a randomized contralateral comparative clinical trial that was performed on 80 eyes of 40 children under 13 y of age undergoing bilateral symmetric strabismus recession surgery in Cairo University Hospitals (Cairo University Specialized Pediatric Hospital–Abu Al Reesh and Kasr Al Ainy Hospital) from the period between October 2015 and April 2016. An estimation of sample size was performed considering a study power of at least 0.8 with an alpha error of 0.05, aiming to detect a difference of 4 mmHg in mean IOP in the postoperative week 6 between the two groups, assuming a standard deviation (SD) of 4 mmHg. On the basis of this estimation, a total of 17 eyes in each group were found to be adequate, and considering a total of 20% dropout during the follow-up, the recruitment of at least 20 study subjects in each group was targeted. The study was approved by the local Institutional Review Board in our institution, and parent/guardian informed consent was obtained for all children. In our study, we selected strabismus surgery being an extracocular surgery to overcome the possible risk of IOP elevation secondary to postoperative inflammation. Surgery included only muscle recession to overcome the concern that muscle resection during the strabismus surgery may lead to an IOP rise and only one muscle was operated on in each eye. Our study was designed to reduce confounding variables that may contribute in causing postoperative IOP elevation. All IOP readings were taken using only topical anesthesia, and this is to eliminate the effect of local general anesthesia, and sedation on IOP. To minimize the effect of individual variation in the corticosteroid response on our results, we instilled two different topical corticosteroids, one in each eye of the same patient.

CONCLUSION

Corticosteroid (anti-inflammatory) medicines are used to treat a wide range of disorders. Steroids, regardless of dosage or route of administration, regularly and problematically generate clinically meaningful adverse effects. The most important adverse effect of corticosteroid use is hypertension, which must be considered when determining a patient’s treatment plan because it raises the risk of cardiovascular disease and other consequences. Corticosteroid clinical use should be the primary focus of evidence-based prescribing. Corticosteroid discontinuation is difficult due to a number of dangerous adverse effects, some of which are life-threatening. As a result, deciding whether to administer corticosteroid medication requires a careful assessment of the relative risks and benefits for each patient.

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CONFLICTS OF INTERESTS

Declared none

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