Author's response to reviews

**Title:** Ketorolac topic. A therapeutic possibility in the Retinopathy of Prematurity? Retrospective cohort study

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PDF covering letter
RETINOPATHY OF THE PREMATURE: THERAPY WITH TOPICAL KETOROLAC.
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Summary:
Objective: To evaluate whether topical ketorolac diminishes the progression of Retinopathy of the Premature (ROP) to severe stages that have an impact on the visual capacity of the child.
Methods: Research of retrospective cohort, design before-and-after, comparing the need for cryotherapy for ROP between the groups of preterm newborns of less than 1250 g. or 30 weeks of gestational age (eg) that had high-risk ophthalmological signs to develop ROP or initial ROP and that were dealt with topical ketorolac during the years 2001 and 2002 and the preterm children of similar characteristics admitted to the HUMN of Córdoba, Argentina during 1999 and 2000, without treatment.
Results: Forty-three children received treatment and 35 children were in the control group. Of the children who received treatment one (2.3%) developed threshold of ROP and cryotherapy was performed. In the control group 6 (17%) needed cryotherapy, the difference of incidence shows: OR= 0.12, interval of confidence of 95%= 0 to 0.85 (P = 0.041). Adverse effects attributable to the ketorolac were not detected.
Conclusion: the use of ketorolac in ophthalmic drops diminished the incidence of severe forms of ROP and the requirements of retinal ablation. It seems to be well tolerated by preterm children and it would not interfere with its systemic balance. This first experience with topical nsad to diminish the progression of ROP only points out the possibility of developing a new therapeutic tool in this devastating disorder, and requires the realization of randomized clinical trials to demonstrate its efficacy and safety.
Key words: Retinopathy of the Premature (ROP), Ketorolac topic, criotherapy, preterm newborns, non-steroid antiinflammatory drugs (nsad).

Introduction:
Retinopathy of premature (ROP) is one of the most frequent avoidable causes of blindness in children. (1) In countries with Infant Mortality Rates between 10 and 60/1000 ROP this now emerging as the greatest cause of child blindness. (2)(3)

In Córdoba, Argentine, the population of schools for visual disabled children is of 177 children. Of them 107 (60.5%) had ROP. (4) Similar prevalences are found in other regions of Argentina and Chile. (5) (6)

Patients at risk are premature newborns of very low weight and those which receive oxygen therapy.(7) In those prematures of less than 32 weeks the vascular structure of the choroid is complete in early periods of fetal life and is the circulatory support of the sensitive layers of the retina but, the highly vascularized choroid tissue lacks capacity of self-regulation and cannot control the O2 offered to the tissues by greater blood flow or the increases in the PaO2. (14)

The hiperoxia is particularly toxic for the tissues of immature individuals who have not totally developed their antioxidant defenses, as the enzymatic systems dismutase superoxid, catalase and peroxidase glutation. (17) (15)

The first phase of the disease is characterized by the oxidative injury that damages the endothelium and obliterates the vessels in formation. The second phase is characterized by the reactivation of vascularization of the retina and its success depends on the magnitude of the endothelial injury by peroxidation and on the level of overstimulation generated by the ischemia of the sensitive tissues that liberate various factors of cellular and vascular growth. (14)(17)(2)

This neovascularization, the active ROP, finds the fusiform cells necrosed or very altered and an injured and distorted retina that hinders the extension and normal ramification of the vessels. Most of the time vascularization succeeds in covering the entire internal surface of the retina but in severe forms a process of anomalous and aggressive capilarization is generated, a liberation of inflammation mediators, and cicatrization with retraction which would cause disalignments or detachment of the retina of its position choroid. (8) (27)

The categories Pre threshold and Threshold of ROP (18) are summarized descriptions of severe degrees of the disorder with a prognostic value. “Threshold of ROP” has an observed rate of
47% in progression to detachment of retina or disalignments in the stain, with its consequent blindness. In this stage ablation of the avascular retina is recommended to eliminate the stimulus that sustains aggressive vascularization. A 25% of the times the harm to the posterior pole is prevented, losing the peripheral visual capacity. (19) The installation of the stadium Prethreshold has been linked to bad results in the visual function: reduction of sharpness, short-sightedness, amblyopia, etc. (20)

Many research projects have been conducted to try to diminish the progress of ROP by using antioxidants as vitamin E (9), D penicillamine (10) or allopurinol (11), reduction of exposure to light (12) and supplementation of oxygen (13), with little encouraging results.

The early use of corticoids in preterm children to prevent chronic pulmonary disease showed that it helped to diminish a 34% the incidence of severe forms of ROP: RR 0.76 (0.59 to 0.98) as a secondary result of the analysis. (21) The supplementation of Inositol to diminish the SRD in preterms showed as a secondary result a reduction of severe ROP RR 0.09 (0.01-0.67) (22)

The active disease appears in the premature about 4 to 8 weeks after birth, in that period the levels of the factor of vascular growth would increase, as well as other chemical mediators of inflammation as PAF, PGs, and eicosanoids in the retina which would put again under way the process of vascularization that had stopped in the period of oxidative injury. This vascularization has now the characteristics of degeneration and invasion with consequent inflammatory and healing response. (8)(14)(23)(24)

In models of animal experimentation it was possible to diminish the degree of retinal neovascularization with indometacin (25), dexamethasone (26), rofecoxib (27), and bucillamina (antiinflammatory similar to D penicilamina) (28), and increased activity of ciclooxygenase 2 (COX2) was demonstrated in vessels of neoproliferation in retina poshiperoxigenation and the way its inhibition reduced the neovascularization a 37%. (27)

Acting in the active revascularization phase with an antiinflammatory the intensity of neovascularization could be reduced as well as the number of children who reach the severe stages
of ROP with sequelae in their vision. An inhibitor of Cox, which does not generate systemic effects and limited only to an intraocular action could achieve that objective.

**Ketorolac** is an NSAD with moderate antiinflammatory and antipyretic action and a powerful analgesic action, with more than 25 years of presence in the pharmacopeia. It is derived from indometacin. Its mechanism of action is developed through the interruption of the synthesis of prostanoids, inhibiting the way of cyclooxygenase in arachidonic acid metabolism; in this way the tissue levels of prostaglandin F2alpha and tromboxano B2 decrease. Its adverse reactions are linked predominantly to their inhibitory action of platelet aggregation. It does not alter the platelet count, the APP, nor the KPTT. (29) Like other nsad, at renal level it reduces blood flow by a decrease of prostaglandins with action on the glomerular system, being able to increase levels of creatininemia, BUN and serum potassium upon diminishing the effective diuresis. (29)(30)

High digestive hemorrhage is the principal digestive adverse reaction. Nervous and the cardiovascular systems are not generally affected by the use of ketorolac to habitual doses. (42)

**Ketorolac topical** is of frequent use, prolonged and safe in older adults with retina disorders mediated by PGs. Ketorolac ophthalmic topic 0.5% to a dose of a drop (0.25 mgr) every 6 hours during 3 to 6 months is used to diminish the Cistoid Macular Edema that complicates the surgery of cataracts. The surgical trauma would produce a liberation of prostaglandins and other inflammation mediators that cause increase of permeability of the perifoveales capillaries of the retina. In this pathology ketorolac has proved to be effective in diminishing the macular edema and improving the visual sharpness, giving proof that their conjunctival instillation produces effects on the most internal layers of the eye. (31)(32)(33) The ophthalmic use of ketorolac only reports occasional episodes of discomfort and ocular burning. (34)

The use of the ophthalmic solution in pediatrics is frequent as analgesic in corneal abrasions, allergic and post surgical conjunctivitis. (35) (36) The FDA recognizes its indication for conjunctival allergy, ocular pain, post surgical ocular inflammation, ocular pruritus and photophobia. (37). Ketorolac administered as conjunctival topic diminishes E2 prostaglandin concentration in aqueous humor, without modifying the intraocular pressure. (37) Ketorolac also
proved better than corticoids in the function of maintaining the integrity of the blood-aqueous humour barrier. (38) And it is effective in uveitis induced by tumorous necrosis factor. (39) The ketorolac is unquantifiable in plasma when administered in topically ophthalmic form. (37)

On the basis of the experimental evidence and this physiosiopatogenic rationality we utilize ketorolac in ophthalmic drops to attempt to diminish the progression and severity of ROP in the preterm newborns treated in the NICU of our hospital. The objective of this retrospective analysis is to know whether the effect searched for was achieved, its magnitude and if the use of these ophthalmic drops was innocuous.

**Population and Methods.**

This is a research of retrospective cohort. We reviewed the clinical registers of preterm children less than 1250 g. or 30 weeks of gestational age admitted to the Neonatal Intensive Care Unit (UCIN) of the Service of Neonatology of the University Hospital of Maternity and Neonatology of the UNC, Córdoba (Argentina) between 01 January of the year 1999 and 31 December 2002.

Two differentiated groups were constituted, an “exposed group” of preterm newborns admitted from 1 January 2001 until 31 December 2002, who received topical ketorolac due to high risk for ROP or ROP of initial course. And an “unexpensed group” of preterms admitted to the NICU between 1 January 1999 and on 31 December 2000, who did not receive treatment with ketorolac.

There were no differences among the groups regarding the policy of care that the unit carried out, apart from the daily improvements in neonatal practice. There were no differences either in equipment or in the number of physicians and nurses that took care of the patients in the two periods.

All the children were examined by same ophthalmologists highly experienced in ROP that were consulted by the neonatologists when the children reached the age and the condition for the examination. From this first examination a routine was established for ophthalmic examinations
according to the severity criterion of the findings. The international classification for ROP (18) was used to define the stages of the disease and the ophthalmological signs considered of high risk to develop ROP were: incomplete vascularization of area I, vessels only in area of transition I - II, or anomalous ramification and equatorial incurvation of the vessels in the vascular – avascular junction. (18)(40)

The children of the Kerotolac group who at some time, from the first examination of ophthalmological screening showed ROP of initial course or high-risk signs for ROP were treated with a drop of ketorolac trometamina (0.25 mgrs) every 8hs. in each eye. The mean of beginning of therapy was of 33.5 weeks of gestational age. and it continued until they presented signs of threshold for cryotherapy or resolution of ROP. The parents of these children gave their consent so that their children could receive treatment. Children with major congenital malformations or hemorrhagic, renal or liver alterations, at the time of the indication of the drug were not included.

The variables considered to assess the comparability among both groups were: 1- `birthweight` in three groups: 1250-1001 grs. 1000-751 grs. and <750 grs. 2- Apgar at birth < 6 to the 5 minutes. 3- duration of oxygen therapy: < 10 days, 10–28 days and >28 days. 4- rate of `survival`. 5- Peri–intraventricular hemorrhage (PIVH) => 3 degree. 6- Necrotizing Enterocolitis (NEC) => II degree. 7- Late Sepsis .

The presence of undesirable effects of ketorolac as hemorrhages, oliguresis, local manifestations of intolerance, or of conjunctival infection were also analyzed.

Statistical analysis was carried out through the programs SPSS 8.0 and Stats Direct Statistical Sofware. The exact test of Fischer was applied to assess two-tailed P. Odds ratio (OR) was determined as well as confidence intervals by the exact test of Leddell.

**Results**

During the period analyzed 112 eligible preterms were admitted, 53 in 1999 and 2000 and 59 in the years 2001 and 2002 when topical ketorolac was used. In Table No. 1 the characteristics of the two groups are presented.
Survival percentage was 66% in the first group and 72.8% in the group with ketorolac. In the distribution by weight and its strata an increase of children < of 750 grs in the kerotolac group is observed. The score of Apgar <6 at 5 minutes as a marker of perinatal hypoxia is similar in the both groups. In the ketorolac group the incidence of late sepsis and of NEC was higher and the incidence of PIVH was lower.

Regarding the duration of oxygen therapy, it was longer in the unexponsed group.

In the ketorolac group 45 children were alive at the first ophthalmic control, two died before discharge due to late sepsis, and 43 received treatment with ketorolac. Nineteen children were discharged from the NICU with treatment indication, and continued with ketorolac up to the 44 weeks, when the ophthalmologists considered overcome their risk for ROP.

A child (2.3%) from the group of the 43 preterms treated with ketorolac reached the threshold stage and cryotherapy was performed. In the unexponsed group used as control, the global incidence of threshold ROP was 12% in 1999 and 10.7% in the year 2000. Three children required cryotherapy each year. The incidence of ROP in the survivors of this grupo(1999-2000) was 17%. See Graphic No. 1

Ketorolac showed a reduction in the risk of severe ROP of 88%, OR of 0.12 (0–0.85), with a value of P for two tails for the exact Test of Fisher of 0.041, a statistically significant reduction. An adjustment was made for the variable “duration of the oxygen therapy.” The value of OR corrected by that variable was of 0.18 (0.02–1.39) and the RRR by greater utilization of O2 was of 82%.

Hemorrhages were not observed in the vitreous after treatment with ketorolac. In four cases hemorrhage of the vitreous was already present at the beginning of therapy and these disappeared after 14 days of treatment.

No child presented signs of local intolerance, or infectious conjunctivitis. We did not find hemorrhages in other organs attributable to the drug, or signs of renal failure. Treatment was suspended in none of the cases and all preterms received it up to its interruption due to the resolution of ROP or the indication of cryotherapy.
Discussion

We find in the group exposed to the treatment with topical ketorolac a very important drop in the global incidence of severe ROP, from 11.6% to 1.6%, and of the incidence of ROP in the surviving preterms, from 17% to 2.3%.

The prevalence of severe ROP in our maternity was relatively high, considering that for the year 1998 the Database Vermont-Oxford Network reported an incidence of 9.48% for severe ROP and of 57.2% for ROP of any degree (16), but similar to the reported by other units in our country and in others in a similar situation. (41)(42)(43)

The principal factor implied in the genesis and severity of ROP is the injury due to O2 radicals. We did not have substantial changes in the management of the supply of O2 to the children of our unit in the period studied, neither existed differences with respect to the equipment used to provide the gas nor those in which we measure O2 saturation.

Although there were not modifications in the guides of management of the unit, mortality declined in the last period, which reflects better neonatological care or a better health in our population of patients. But although the reduction in mortality was of 20%, that of severe ROP was of 88%.

No patient in the group that received ketorolac presented oliguric, or signs of renal failure during treatment. There were no hemorrhagic manifestations that could be attributed to ketorolac; hemorrhages observed in the vitreous evolved favorably with the collyrium. Neither local intolerance episodes to the drops nor purulent conjunctivitis among the treated cases were observed.

This retrospective analysis shows that there could exist a heavy impact of the Ketorolac on ROP in the active phase of revascularization, a fact that is also observed in numerous reports of tests in animal models of ROP with NSADs administered systemically. This study can contain sources of biases that could divert these results systematically, however a prospective, controlled and random study on this subject does not exist as yet.
The hypothesis of an inflammatory component in active ROP has been quite recently recognized by experts. However, from the use of D penicillamine for ROP(10) in the eighty up to more recent research works with inhibitors of COX2(27) show that antiinflammatorys, steroid or not, apparently have an impact on the prevalence of ROP. And recently Neufeld et al. found high plasmatic profiles of tumorous necrosis factor (TNF) and other citokuines during the phase of installation of the pre threshold stage for ROP. (46)

Today we can recognize the mechanisms of cellular and molecular injury of O2 radicals and how these trigger responses of inflammation through the way of the COXs and others. (14)(15)

Cox has a strong angiogenic action in the normal development of the retina and in the model of feline ROP. The inhibition of COX2 diminishes the angiogenesis in cancer, rheumatoid arthritis, and granulomata. (44) (27) The ganglion cells of the retina secrete PGs that would interact with angiogenic substances as a factor of endothelial and vascular growth (VEGF) and a factor of insuline like growth in models of hiperoxic experimental retinopathy. The neovessels express a greater concentration of COX2 and the inhibitors of COX2 stop the angiogenesis mediated by VEGF, which is the principal factor implied in the neovascularization and which would be regulated by the PGs secreted by ganglion cells of the retina and endothelial cells. (45)(27)

The hiperoxia induces the liberation of tumorous necrosis factor (TNF) with a powerful inflammatory action; by interfering the production of TNF dexamethasone would act attenuating the manifestations of retinopathy by hiperoxia. (26) The topical ketorolac was very effective in neutralizing uveitis generated by experimental infection with monoclonal TNF or bacterial endotoxins. (33)(47)(48)

The topic of ketorolac has proved safe in adult patients with cistoid macular edema who often need it during periods of over six months and it seems to be us safe also in preterm newborns.

Conclusion

Apparently the reduction of the incidence rate of threshold ROP in the two last years reviewed would be caused by the systematic use of topical ketorolac. Probably topical ketorolac
diminishes the reaction of vascular neoproliferation and its inflammatory component giving more possibilities for the vascularization to cover the retina without damaging it and without showing side effects of importance among preterm newborns.

**Implications for research and practice.**

ROP is a problem that modern medicine has generated upon achieving the survival of small preterm children and which has not been able to resolve. Around 2% of the children of less than 1500 grs. of weight lose sight due to this pathology.

With the available interventions, once reached the severe stages we can prevent the loss of sight in little more than 70% of the cases. Ablationist therapy of the retina is being reevaluated in order to determine the optimal moment for its use (20), but encompasses in itself the conviction that we have already lost most of the battle against ROP.

The use of NSADS by conjunctival way, without risk of systemic actions, and with preventive effects of the severe stages of ROP would make it possible to take an important step forward in order to sustain the right to light, as promoted by WHO in its initiative VISION 2020.

We believe that there exists enough evidence to conduct a controlled and random study to evaluate this, as well as other antiinflammatories that could act beneficially in ROP.

Finally we want to warn that our experience points out what we interpret as the sense of an effect and an apparent innocuousness, but that is very premature to recommend its use before new and further studies are performed.