Author's response to reviews

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

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PDF covering letter
Title: RETINOPATHY TREATMENT OF THE PREMATURE WITH TOPICAL KETOROLAC.

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Summary:

Objective: Evaluate if the topical ketorolac diminishes the progression of Retinopathy of the Premature one (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 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 2001 and the preterm children of similar characteristics entered the HUMN of Córdoba, Argentina during 1999 and 2000, without that treatment.

Results: Forty-three children received treatment and 35 children were in the control group. Of the children who received treatment 1 (2.3%) form developed threshold of ROP and cryotherapy received. In the control group 6 (17%) needed cryotherapy, the difference of express incidence: OR= 0.12, interval of confidence of 95%= 0 to 0.85 (P = 0,041). Adverse effects attributable to the ketorolac were not registered.

Conclusion: the use of ketorolac in ophthalmic drops diminished the incidence severely of ROP and the requirements of retinal ablation. It seems to be well tolerated by the children preterm and it would not interfere with its systemic balance. This first experience with topical aines to only diminish the progression of ROP points out the possibility of developing a new therapeutic tool in this devastating disorder, and requires the realization of Random clinical research to demonstrate its efficacy and safety.

Key words: Retinopathy of the Prematurity (ROP), Ketorolac topic, crioterapy, newborns preterms, non-steroid antiinflammatories (nsad).
Introduction:

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

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

The children with risk are premature of very low weight and those which receive oxigenoterapea.(7) In the premature less than 32 weeks the vascular structure of the choroid this complete in early periods of fetal life and is the circulatory support of the sensitive layers of the retina but, the highly chorioid tissue vascularizado lacks capacity of self-regulation and cannot control the O2 offered to the // tissues by greater blood flow or increases of the PaO2. (14)

The hiperoxia is toxic particularly for the tissues of immature individuals that their defenses completely do not have developed antioxidant, as the `enzymatic` systems superóxido dismutase, catalase and glutation peroxidase. (17) (15)

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

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

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

Many research projects have been conducted in order to attempt to diminish the progress of the ROP utilizing antioxidants as vitamin E (9), D `penicillamine’ (10) or `allopurinol’ (11), reduction of the exposure to the light (12) and supplementation of I oxygenate (13), with results little encouraging.

The utilization of Corticoids in form early in children preterm in order to prevent chronic pulmonary disease showed that disminuía in 34% the incidence of severe forms of ROP: RR 0.76 (0.59 to 0.98) as a secondary result of the analysis. (21) Also supplementation of Inositol to diminish the RDS in preterms showed as a result secondary reduction of ROP severe RR 0.09 (0.01-0.67) (22)

The active disease is revealed in the premature to the 4 or 8 weeks after the birth, in that period they would increase the levels of the factor of vascular growth and other chemical mediators of the inflammation as PAF, PGs, and eicosanoides in the retina that would put again under way the process of vascularization that had stopped itself in the period of oxidative insult. This vascularization now has 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 neovascularización with `indometacin` (25), `dexamethasone` (26), rofecoxib (27), and bucillamina (similar antiinflammatory to Dpenicilamina) (28) was demonstrated the activity increased of ciclooxigenasa 2 (COX2) in glasses of neoproliferación in retina poshiperoxigenación and as its `inhibition` reduced the neovascularización in 37%. (27)

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

The ketorolac is an AINE with moderate antiinflammatory and antipyretic action and powerful analgesic action and with more than 25 years of presence in the pharmacopeia, is derived from the indometacinA. Its action mechanism is developed through the interruption of the synthesis of prostanoides upon inhibiting the way of the ciclooxigenasa in the arachidonic acid metabolism, in this way they decrease the tissue levels of prostaglandin F2alfa and tromboxano B2. Its adverse reactions are linked predominantly to their inhibitory action of the platelet aggregation. It does not alter the platelet count, the APP, nor the KPTT. (29)

Como others aines, at renal level reduces the blood flow by reduction 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)

The high `digestive` hemorrhage is the principal `digestive` adverse reaction. The nervous system and the cardiovascular do not tend to be affected by the use of ketorolac to habitual doses. (42)

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

The utilization in pediatrics of the ophthalmic solution is frequent as analgesic in corneal abrasions, allergic, and posquirúrgicos conjunctivitis. (35) (36) The FDA recognizes its indication for conjunctival allergy, ocular pain, ocular inflammation posquirúrgica, ocular pruritus and photophobia. (37) The ketorolac administered as conjunctival topic diminishes the prostaglandin concentration E2 in aqueous humor, without modifying the intraocular pressure. (37) Ketorolac also appeared higher than corticoids in the function to maintain the integrity of the blood-humor barrier aqueous. (38) And it is effective in uveitis induced by `tumor` necrosis factor. (39) The ketorolac is unquantificable in plasma when it is administered topically ophthalmic. (37)

On the basis of the experimental evidence and this fisiopatogénica rationality we utilize ketorolac in ophthalmic drops to attempt to diminish the progression and severity of ROP in the children preterm served in the NICU of our hospital. The objective of this retrospective analysis is to know if the sought effect was achieved, which was its magnitude and if the utilization of these ophthalmic drops was innocuous.

**Population and Methods.**

It is research of retrospective cohort. The clinical registries of children were reviewed preterm 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.

They were constituted two differentiated groups, an “exposed group” of newborns preterm admitted since 1 January 2001 until 31 December 2002 and that received ketorolac topical by high risk of ROP or ROP of course initiates. And an “unexposed group” of preterms admitted to the NICU between 1 January 1999 and on 31 December 2000, that did not receive treatment with ketorolac.

There was not differences among the groups with respect to the policy of care that the unit carried out, beyond the best daily of the neonatal practice, neither there was differences in the equipment nor in the number of physicians and nurses that served the patients in the two periods.

All the children were examined by experienced ophthalmologists in ROP that were cited by the neonatologists when the children acquired the age and the condition for the examination. From this first examination an ophthalmic examination routine was established according to the criterion for severity of the findings. The international classification of ROP (18) was utilized to devise the stages of the disease and it was considered as high-risk ophthalmological signs to develop ROP to: incomplete vascularization of area I, only glasses in area of transition I - II, or anomalous ramification and equatorial incurvation of the glasses in the vascular union–avascular. (18)(40)

The children of the group ketorolac (exposed) that at some time, from the first examination of screening ophthalmological, presented ROP of initial course or high-risk signs to develop ROP were treated with a drop of ketorolac trometamina (0.25 mgrs) every 8hs. in every eye. The average of beginning of the treatment it was of 33.5 weeks of eg. and the treatment continued until they presented signs of threshold for cryotherapy or resolution of ROP. The parents of the children gave consent so that her children received the treatment. The local bioetica committe approved the therapeutic test. There was not
included in this analysis children with greater congenital malformations or that presented hemorrhagic alterations, renal or liver at the time of receiving the indication of the drug.

The variables considered to assess the comparability among the 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- Hemorrhage peri–intraventricular (HPIV) => 3 degree. 6- Enterocolitis Necrotizing (NEC) => II degree. 7- Sepsis late.

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

The statistical analysis was carried out through the programs SPSS 8.0 and Stats Direct Statistical Software, there was applied the exact test of Fischer in order to assess P two-tailed, there was determined odds ratio (OR) and was determined confidence intervals by the exact test of Leddell.

**Results**

In the period analyzed they admitted 112 preterms, 53 in the years 1999 and 2000 and 59 in the years 2001 and 2002 in that was utilized ketorolac topical. In the Table No. 1 is presented the characteristics of the two groups.

**TABLE No. 1**

The percentage of `survival` was 66% in the first group and of 72.8% in the group with ketorolac. In the distribution by weight and its strata is observed an increase of children < of 750 grs in the group ketorolac. The score of Apgar <6 to the 5 minutes as perinatal hypoxia marker is similar in the two groups. In the group ketorolac was greater the incidence of late sepsis and of EN and child the incidence of HPIV.

With respect to the duration of the oxygen therapy, it was greater in the unexponsed group.

In the group ketorolac 45 children arrived live to the first ophthalmic control, two died before the discharge by late sepsis and 43 received treatment with ketorolac.
Nineteen children were discharged of the UCIN with the treatment and continued with ketorolac until the 44 weeks, moment in which the ophthalmologists considered surpassed their risk of ROP.

A child (2.3%) of the 43 preterms treated with ketorolac reached the stage threshold and I am carried them out cryotherapy. In the unexpansed group utilized of control the global incidence of ROP threshold was 12% in 1999 and 10.7% in the year 2000, three children required cryotherapy in every year. The incidence of ROP in the survivors of this grupo(1999-2000) was 17%. See Grafico No. 1

GRAPH NO. 1

The ketorolac showed a reduction at the risk of the serious ROP of 88%, OR of 0.12 (0−0.85), with a value of P for two lines by 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 (relative risk reduction) by greater utilization of O2 was of 82%.

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

No child presented signs of local intolerance, nor infectious conjunctivitis. We do not find hemorrhages in other adjudicables organs to the drug, nor 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 fall in the global incidence of severe ROP from 11.6% to 1.6% and of the incidence of ROP in the children surviving preterms from 17% to 2.3%.
The prevalence of severe ROP in our maternity was relatively high, considering that for the year 1998 on the basis of Data of the Network of Vermont-Oxford 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 similar. (41)(42)(43)

The principal factor implied in the genesis and severity of the ROP is the injury due to radicals of O2. 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 utilized to provide the gas nor in which we measure the saturation of O2.

Although there were not modifications in the guides of management in 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 of the group that received ketorolac presented biochemical oliguresis, nor signs of renal decision during the same. There were not presented hemorrhagic manifestations that we could attribute to ketorolac, the hemorrhages observed in the vitreous evolved favorably with the collyrium. Neither local intolerance episodes were presented to the drops nor purulent conjunctivitis among the treated cases.

This retrospective analysis shows that there could exist a heavy impact of the Ketorolac on the ROP in the active phase of revascularization, fact that also is observed in the numerous reports of tests in animal models of ROP with AINES administered systemically. This study can contain sources of biases that could divert these results systematically, however there does not exist still a prospective, controlled and random study on this subject.

The hypothesis of an inflammatory component in the active ROP is quite recently recognized by the experts. However, from the utilization of D `penicillamine` for ROP(10) in the years 80’ up to more recent research with inhibitors of COX2(27) show that antiinflammatories, steroid or not, apparently have an impact on the prevalence of ROP.
And recently Neufeld et al. found high `plasma` profiles of factor of `tumor` necrosis (TNF) and others citoquinas during the phase of installation of the stage preumbral of ROP. (46)

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

The Cox has loudly angiogenic action in the normal development of the retina and in the model of ROP feline. The `inhibition` of COX2 diminishes the angiogenesis in cancer, rheumatoid arthritis, and granulomata. (44) (27) The `nodal` cells of the retina secrete PGs that would interact with substances angiogénicas as factor of endothelial and vascular growth (VEGF) and factor of growth alike-insulin in models of retinopathy hiperoxica experimental. The neovasos express greater concentration of COX2 and the inhibitors of COX2 stop the angiogenesis mediated by VEGF that is the principal factor implied in the neovascularización and that serious regulated by the PGs secreted by `nodal` cells of the retina and endothelial cells. (45)(27)

The hiperoxia induces liberation of `tumor` necrosis factor (TNF) with powerful inflammatory action; interfering the production of TNF would act the `dexamethasone` that attenuates the manifestations of retinopathy by hiperoxia. (26) The topical ketorolac was very effective in order to neutralize uveitis generated by experimental infection with monoclonal TNF or bacterial endotoxins. (33)(47)(48)

The topic of ketorolac has been shown safe in adult patients with macular edema cistoide that often need it during periods of over six months and it seems to us safe also in newborns preterm.

**Conclusion**

Apparently the reduction of the incidence rate of ROP threshold in the last two reviewed years would be caused by the systematic use of ketorolac topical. The topical ketorolac probably diminishes the reaction of vascular neoproliferación and its inflammatory component giving more possibilities that the vascularization covers the retina.
without damaging it and it did not manifest side effects of importance on the newborns preterms.

Implications for research and the practice.

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

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

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

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

Finally 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 state that its utilization is recommendable without new and better studies.

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