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An evaluation of the efficacy of indomethacin in experimentally induced acute sinusitis in rats

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Abstract. – OBJECTIVE: We evaluated how efficacious indomethacin, at two different doses, is in the treatment of an experimental model of sinusitis in rats.

MATERIALS AND METHODS: Twenty-one Wistar albino rats (all male) were sorted at random into one of three groups: 1st group (n=7) was placebo. 2nd group (n=7). These rats had sinusitis induced experimentally, following indomethacin 3 mg/kg, 5 days was administered to them. 3rd group (n=7). These rats had sinusitis induced experimentally, following indomethacin 6 mg/kg, 5 days was administered to them. The animals' sinonasal mucosae were examined histopathologically by standard light microscopy.

RESULTS: Experimental sinusitis was observed in the 2nd and 3rd groups, but not in the rats administered a placebo. Although the inflammatory features of sinusitis were found to be significantly decreased in the animals administered indomethacin 3 mg/kg (the 2nd group), this anti-inflammatory effect was even greater in the 3rd group, where indomethacin 6 mg/kg had been administered. Indomethacin at either dose was superior to placebo in reducing inflammatory features of sinusitis.

CONCLUSIONS: Topical use of indomethacin nasal drops decreased the inflammatory features in experimentally induced acute sinusitis. Moreover, a higher dose of indomethacin (6 mg/kg) was more efficacious than a lower dose (3 mg/kg). The present study is valuable as an initial step in showing the need to undertake human trials to see the effect of indomethacin nasal drops on sinusitis in humans. In acute rhinosinusitis, the use of topical anti-inflammatory drops may help to decrease the symptoms and may be used adjunctively with antibiotic treatment.

Key Words:
Experimental sinusitis, Rats, Indomethacin drops, Topical use.

Introduction

In the majority of countries, rhinosinusitis occurs with high frequency, resulting in a significant demand for healthcare services and a decrease in individual productivity[1-4]. Annually, between 6 and 15% of the population experiences an acute episode of rhinosinusitis, typically as a complication of coryza. Acute rhinosinusitis (ARS) generally resolves spontaneously, although there are reports of cases where fatal or potentially fatal complications have arisen[5]. ARS is amongst the most frequent reasons for antibiotic use, hence, in the current climate of an increasingly alarming growth in antibiotic resistance, appropriate treatment is more essential than ever[6,7].

The criteria used to diagnose ARS in adults[6] are the abrupt onset of a minimum of two symptoms from the following list, which must include either a blocked nose (congested or obstructed) or rhinorrhoea (*via* the nostrils or the nasopharynx): pain or pressure felt over the face and hyposmia or anosmia lasting no longer than 12 weeks. If ARS is recurrent, there should be periods without these symptoms, which may be confirmed by face-to-face or remote consultation[6].

For chronic rhinosinusitis (CRS), the essential features are an obstructed or congested nose, rhinorrhoea (*via* the nostrils or the nasopharynx), hyposmia, or anosmia, and a feeling of pain or

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pressure over the face. The frequency of these particular symptoms varies depending on whether the sample selected consists of patients attending surgeries, the general population, hospital clinics or those awaiting nasal operations[6]. The degree of severity also varies, when comparing patients attending outpatient clinics and those admitted for surgical interventions[6].

Blockage to the nose and olfactory and gustatory functional alteration predominate in terms of frequency and severity in cases of CRS with nasal polyposis, whilst in CRS not associated with polyp formation, the severity of pain and rhinorrhoea matches the severity of olfactory and gustatory functional alteration[8,9].

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) based on the indole moiety. Indomethacin undergoes enterohepatic cycling and has a complex metabolic pathway leading to inactivation. The effect *in vivo* is to inhibit the metabolism of prostaglandin, an effect that occurs even when the drug is circulating at an extremely low level. Prostaglandin inhibition is measurable with all of the preparations currently marketed. The agent is 85% bioavailable. Indomethacin is available as a capsule and as sustained-release products, namely Indocin SR and Indos. These agents all appear to offer equal therapeutic benefit[10].

The study was performed to evaluate how efficacious indomethacin is in the treatment of an experimental model of sinusitis in rats. There were two dosages employed: 3 mg/kg and 6 mg/kg, both in aerosolized droplet form. Then, a histopathological assessment of the dissected rat sinuses in the intervention and control groups was followed.

Materials and Methods

The experiment was undertaken at the Eskisehir Osmangazi University. The animals were housed and prepared for the experiment at the Medical and Surgical Research Unit of the University, known as TICAM. The principles regarding the treatment of experimental animals outlined in the AAALAC International were followed at every stage prior to and during the experiment itself.

Animal Subjects

The experiment called for the use of 21 rats. These were Wistar albino strains, all-male and in good health adult rats. The protocol to be followed for the experiment underwent review and approval by the Animal Experiments Local Ethics Committee, operating under the auspices of the University Rectorate. Approval was granted on 23rd Jan 2019 *via* decree number 706/2019. The approved protocol was used in all procedures involving the rats.

The animals were accommodated under conditions of fixed temperature, humidity, and light for one week prior to the experiment. The temperature was maintained at a steady 20-22 Celsius, with a relative humidity of 55%. The animals were kept in alternating 12-hour periods of light and darkness. They had free access to a standard rat feedstuff in pellet form and tap water. The rats were monitored externally for changes in appearance and weight loss or gain. Any alterations were noted.

Experimental Design

The animals were allocated by a randomization procedure to one of three groups:

1. Group 1 (Placebo/control): these animals were administered a nasal formulation without active ingredients (n=7)
2. Group 2 (Sinusitis+, indomethacin lower dose): these animals had sinusitis experimentally induced, after which indomethacin 3 mg/kg was administered by nasal spray (n = 7).
3. Group 3 (Sinusitis+, indomethacin higher dose): these animals had sinusitis experimentally induced, after which indomethacin 6 mg/kg was administered by nasal spray (n = 7).

For each group, the mode of administration was designed to maximize the delivery of the agent.

In the 2nd stage of the experiment, bacteria were inoculated into the rats in groups 2 and 3 to create experimentally induced acute sinusitis *in vivo*. Bacterial organisms belonging to the *Streptococcus pneumoniae* ATCC® 10015 standard strain were purchased commercially and cultured on Mueller Hinton agar containing 5% sheep blood.

A Merocel nasal pack measuring 2 mm × 3 mm × 20 mm was inserted into the left nasal cavity of the rats for one hour for a period of between 4 and 8 days. The *S. pneumoniae* bacteria were suspended in 0.1 mL sterile, physiological saline to a dilution matching the 3rd McFarland turbidity standard. The nasal pack was soaked in this bacterial solution before being inserted into the rat's

nasal cavity. A period of 72 hours was permitted to elapse, in which sinusitis was anticipated to occur. After this period, it was noted that purulent discharge was coming from the nose. The culture of this discharge confirmed that it contained *S. pneumoniae* organisms.

For the third stage of the experiment, the animals in groups 2 and 3 had already developed sinusitis. A nasal spray was used to administer indomethacin to the animals. Those in group 2 received a dose of 3 mg/kg, whereas the rats in group 3 received a dose of 6 mg/kg. Treatment was given for 5 days.

The fourth stage of the experiment involved waiting 24 hours after administration of the final dose. The rats were painlessly euthanased by being injected with pentothal 80 mg/kg. They were then dissected to remove the mucosa from the maxillary sinuses as well as the mucosa from the nasal turbinates and nasal interior.

Procedure for Histopathological Examination

The paraffin-embedded specimens were sectioned at a slice thickness of 5 microns, then placed onto adhesive slides. These slides were dried by placing them in a slide dryer at 37 Celsius overnight and then for 20 minutes at 60 Celsius. The remaining paraffin was cleared by a double immersion into xylene, each lasting 20 minutes. The tissue was dehydrated by passing through ethanol solutions of increasing strength (70, 80, 96, and 100% ethanol). The stain used was hematoxylin-eosin. The person rating the slides was blinded to which group the sample came from. In all cases, at least ten microscopic fields were examined and any changes from normal appearance were graded[11]. An Entella Olympus BH-2 light microscope was used for histological examination and digital images were obtained with an Olympus DP-70 camera.

During histological examination, mucosal damage and cilia loss, hyperplasia of Goblet cells, inflammation, vascular congestion, vascular dilatation, and subepithelial glandular atrophy were evaluated by light microscopy[11].

Results

Histopathological Grading Outcomes

There was evidence of sinusitis in all the animals belonging to groups 2 and 3, but not in the control rats.

For the animals in group 2, which received indomethacin at a dose of 3 mg/kg, there was evidence of improvement in the inflammatory process associated with sinusitis. In the animals in group 3, which received the higher dose of 6 mg/kg, there was an even greater resolution in the markers of inflammation.

The histopathological findings for each group of rats are summarised as follows:

1. Control group animals (Group 1): normal structural appearances were observed in the sinonasal epithelium. (Figure 1A1, A2, A3)
2. Group 2 animals: the sinonasal epithelial architecture is almost normal, although partial thickening of the vascular walls in the connective tissue was observed. Although the mild epithelial injury was noted in some areas of the epithelium, in general, a nearly normal epithelial structure is observed. In addition, some areas of hemorrhage could be seen within the connective tissue (Figure 2B1, B2, B3).

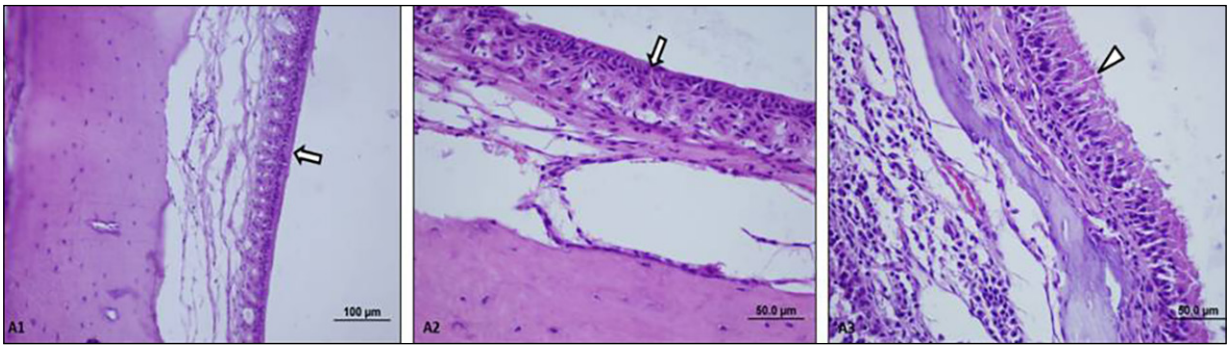

Figure 1. Control group: Olfactory (olfactory) epithelial structure () A1, A2) and respiratory epithelial structure (►) (A3) were observed in normal histological structure (HE, scale bar: 100 µm, scale bar: 50.0 µm) on light microscopic examination.

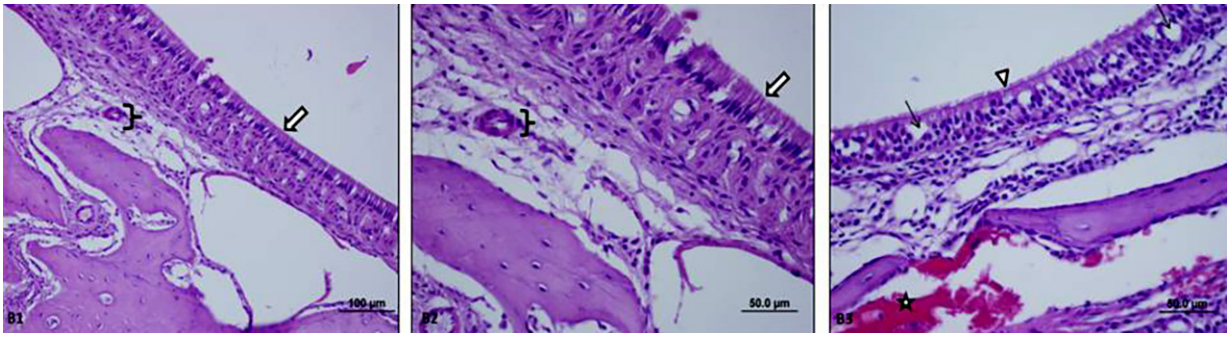

Figure 2. 3 mg/kg nasal indomethacin group: On light microscopic examination, the olfactory (olfactory) epithelium structure is almost normal () (B1, B2) partial thickening of the vascular walls in the connective tissue () (B2). Although little damage is observed in some areas of the respiratory epithelium (→), generally nearly normal epithelial structure is observed (►). In addition, partial hemorrhage is seen in the connective tissue () (B3) (HE, scale bar: 100 µm, scale bar: 50.0 µm).

3. Group 3: On light microscopic examination, the sinonasal epithelium structure is virtually intact. There is a slight injury at most to the respiratory epithelium, which preserves a normal architecture. There are patches of cellular inflammation noted within the connective tissue (Figure 3C1, C2, C3).

Discussion

Rhinosinusitis is a disorder in which inflammation occurs within the mucosal lining of the sinuses and nasal cavity. To diagnose ARS in children, there must be symptoms affecting the upper respiratory tract and involving pyrexia that lasts at least seven to ten days[12].

Rhinosinusitis is a category that comprises a number of discrete disease entities, in particular ARS, recurrent acute rhinosinusitis, and chronic rhinosinusitis (CRS), which can itself be separated into CRS with accompanying nasal polyp formation (CRSwNP) or without accompanying nasal polyp formation (CRSsNP). These conditions all produce similar symptoms, namely a blocked nose, nasal stuffiness, pain or pressure over the face, rhinorrhoea *via* the nostrils or nasopharynx, and loss, or partial loss, of smell for varying durations of time[13-15].

By definition, ARS involves the abrupt onset of symptoms affecting the nose and sinuses linked to an inflammatory process in the nose and sinuses and has a maximum duration of 4 weeks[13,14,16,17]. The symptomatic presentation includes a blocked or stuffy nose, rhinorrhoea, pain or pressure over the face and abnormalities of the sense of smell. The discharge from the nose frequently contains pus and may be a different color from usual. Typically, the discharge comes from one side, although it can also occur on both sides[13,14]. The pain and pressure over the face are of at least moderate severity[18]. Viral or bacterial pathogens may be implicated. When the cause is a virus, ARS rarely lasts longer than ten days, hence, lengthier symptomatic duration suggests a bacterial origin[14,18]. A progressively deteriorating

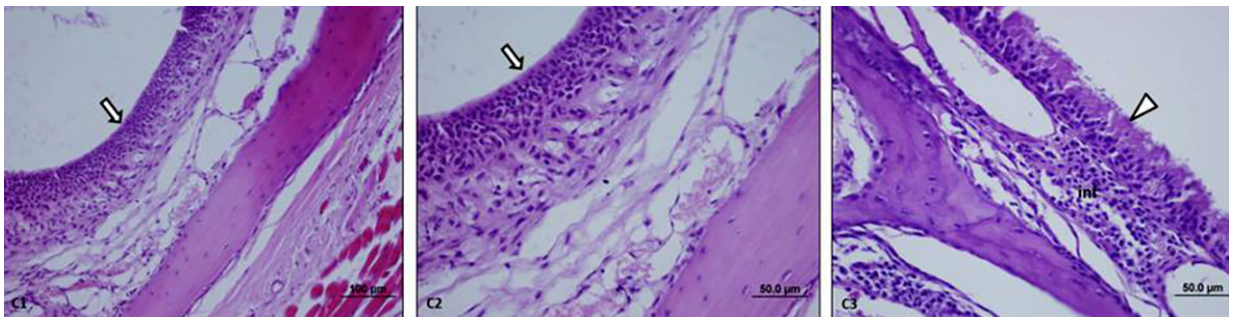

Figure 3. 6 mg/kg nasal indomethacin group: On light microscopic examination, the olfactory (olfactory) epithelium structure is almost normal () (C1, C2) With reduced damage in the respiratory epithelium, generally nearly normal epithelial structure is observed (►). Partial cellular inflammation (inf) is observed in the connective tissue (C3) (HE, scale bar: 100 µm, scale bar: 50.0 µm).

condition over a few days also hints at a bacterial cause[14,18]. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) additionally proposes that pyrexia plus laboratory evidence of inflammation (a raised C-reactive protein or raised erythrocyte sedimentation rate) be performed before diagnosing ARS[14].

Cases of ARS of probable viral origin may usually be managed with symptomatic treatment alone, as the patients will usually recover spontaneously in no more than 7 to 10 days. ARS of bacterial origin is rare – between 0.5 and 2% of cases[14]. Bacterial ARS also often resolves spontaneously. Management may be of symptoms alone, with monitoring of the disease progression, or involve antibiotic medications. It is infrequent for such cases to lead to any serious complications[19].

Our study was designed to assess how efficacious topical nasal indomethacin is in rats with experimentally induced acute bacterial sinusitis. The experiment compared treatment at two different doses of indomethacin, namely 3 mg/kg or 6 mg/kg. For the intervention groups (groups 2 and 3), these doses were applied for 5 days in the form of a nasal spray. During histological examination, sinonasal mucosa was evaluated in terms of mucosal damage and cilia loss, hyperplasia of Goblet cells, inflammation, vascular congestion, vascular dilatation, and subepithelial glandular atrophy by light microscopy.

Experimental sinusitis was observed in the animals of the 2nd and 3rd group, but not in the rats administered a placebo. Although the inflammatory features of sinusitis were found to be significantly decreased in the animals administered indomethacin 3 mg/kg (the 2nd group), this anti-inflammatory effect was even greater in the 3rd group, where indomethacin 6 mg/kg had been administered.

The pathogenetic mechanism of ARS involves the cells of the nasal epithelium triggering an inflammatory response. As cells of the inflammatory system infiltrate the mucosa, there is resulting tissue injury, edema develops, and the vessels become congested and swollen. Fluid builds up surrounding the vessels. The mucosa responds by increasing mucus secretion. These changes result in blockage of the sinus outflow, which either triggers ARS or worsens the existing ARS[6]. It is clear from our results that nasally applied indomethacin, at a dose of either 3 mg/kg or 6 mg/kg has the effect of decreasing the inflammatory response in animals with experimentally induced ARS. Furthermore, the higher dose (6 mg/kg) of the NSAID was even more efficacious than the lower dose (3 mg/kg).

Indomethacin is classified as an NSAID. It inhibits inflammation, is a pain killer, and suppresses pyrexia. NSAIDs as a class consist of chemically dissimilar compounds, on the basis of similar pharmacological effects. In chemical terms, indomethacin is an analog of indole-acetic acid. Its IUPAC name is 1-(p-chlorobenzoyl)25-methoxy-2-methylindole-3-acetic acid[20]. The precise pharmacodynamic characteristics of indomethacin have not yet been elucidated, although the evidence mainly indicates that it exerts its effects by inhibiting non-selectively the cyclooxygenase enzyme (COX), the key catalyst involved in the metabolism of prostaglandin and thromboxane from arachidonic acid precursors. This step limits the rate of the entire pathway[21,22].

Indomethacin non-specifically and reversibly inhibits prostaglandin G/H synthase, one of the two cyclo-oxygenase isoenzymes found in humans. COX-1 is ubiquitous in the majority of tissue types, where it catalyzes the pathway which manufactures prostaglandins and thromboxane A2. Expression of COX-2, in contrast, is triggered when trauma or inflammation occurs[20]. This latter isoenzyme assists in converting arachidonic acid to PGG2, followed by a further step to PGH2. Within the same metabolic pathway, PGH2 undergoes metabolism to become PGE2 and PGI2 (also referred to as prostacyclin). PGE2 has pro-inflammatory and pro-pyretic properties, as well as causing pain. Suppression of PGE2 has a dampening effect on inflammation[21,22].

Chatterjee[23] reported that indomethacin is a nonselective non-steroidal anti-inflammatory drug (NSAIDs) and first-line analgesic in clinical practice. It also has acute anti-inflammatory and immunomodulatory activity. In their experimental study including 12 rats, indomethacin (10 mg/kg) showed a significant inhibitory response in carrageenan and dextran-induced rat paw edema. Moreover, indomethacin (1 mg/kg) showed a significant chronic anti-inflammatory effect (29%) in the arthritic model. They concluded that indomethacin showed acute anti-inflammatory effects besides chronic anti-inflammatory (immunosuppressive) activity. We may conclude that in rhinology practice, the anti-inflammatory effects of indomethacin can be useful for patients with rhinosinusitis having concomitant allergic rhinitis.

Treatment for the symptoms of ARS, regardless of whether it is due to a viral or bacterial pathogen, has the objective of alleviating nasal blockage and discharge, in addition to reducing systemic symptoms, especially pyrexia and lethargy. In appropriate cases, treatment may involve over-the-counter painkillers and antipyretics, washing the nasal cavity with sterile saline and topical nasal steroids[19].

Many cases of ARS secondary to bacterial infection do resolve spontaneously. It has been demonstrated in systematic literature reviews and meta-analytical studies that ARS secondary to the bacterial infection commonly remits in two weeks or less, without the need for antibiotics[24]. If a treatment is required, the authors advise an empirical trial involving either amoxicillin alone or in conjunction with clavulanic acid. This latter combination is appropriate where the risk of antibiotic resistance is high[19].

Treatment of rhinosinusitis typically involves anti-pyretic/anti-inflammatory pharmacotherapy to treat nasal symptoms. Oral antibiotics may also sometimes be employed[12]. Painkillers and antipyretic medications, for example, paracetamol or NSAIDs are appropriate to manage pain and pyrexia[25,26]. The key treatment objective is to unblock the nose and prevent ongoing nasal discharge. Nasal washes with saline and non-prescription painkillers are suitable for this purpose[20].

Krivopalov et al[27] investigated a topical treatment regimen involving Polydexa and phenylephrine. This combination was demonstrated to be clinically beneficial, well-tolerated, improves the flow of mucus away from the sinuses, and be sufficiently safe. The study also utilized a topical nasal spray containing an antibiotic. For our study, a nasal spray containing indomethacin was used topically to treat experimentally induced acute sinusitis. We observed that topical indomethacin decreased the inflammatory histological appearances in acute sinusitis.

Conclusions

Topical use of indomethacin nasal drops decreased the inflammatory features in experimentally induced acute sinusitis. Moreover, a higher dose of indomethacin (6 mg/kg) was more efficacious than a lower dose (3 mg/kg). The present study is valuable as an initial step in showing the need to undertake human trials to see the effect of indomethacin nasal drops on sinusitis in humans. In acute rhinosinusitis, the use of topical anti-inflammatory drops may help to decrease the symptoms and may be used adjunctively with antibiotic treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

The Ethics Committee Approval was obtained from Eskisehir Osmangazi University Rectorship, Animal Experiments Local Ethics Committee (Date: 23.01.2019, Number: 706/2019).

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None.

Authors' Contribution

Y. Kurt: Planning, designing, data collection, literature survey. N. Bayar Muluk: Planning, designing, literature survey, writing, submission. C. Yildirim: Planning, designing, data collection, performing the experiment, literature survey. D. Burukoglu Donmez: Planning, designing, data collection, histologic evaluation, literature survey. K. Erol: Planning, designing, data collection, literature survey. C. Cingi: Planning, designing, data collection, literature survey.

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