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Original Article

Neurotoxic Effects of Aspirin on the Developing Mouse Cerebellum: Implications for Human Health

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Abstract

Introduction: Aspirin is a non-steroidal anti-inflammatory drug (NSAID). Pregnant women often seek relief from common discomforts such as headaches, fever, and arthritis by easily purchasing it over-the-counter. NSAIDs are commonly used during pregnancy, especially for managing chronic conditions such as inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy. In addition, aspirin may be prescribed for obstetrical complications such as preterm labor and polyhydramnios. However, before prescribing long-term aspirin therapy, health-care professionals carefully evaluate the benefits against the potential complications associated with its use. Despite the extensive use of aspirin during pregnancy, there is limited literature available on its potentially harmful effects on fetal development. Therefore, the present study aims to address this knowledge gap by investigating the teratogenicity of aspirin.

Materials and Methods: Pregnant Swiss albino mice were divided into two groups of 151 mice each: control and treated. Aspirin was given to the treated group at a dose of 100 mg/kg body weight from the 3rd to the 5th day of gestation. The control group received an equivalent amount of tap water. The mouse from each group was sacrificed on the 19th day of gestation. After fixation in a 10% neutral formalin solution, the brains of the fetuses were dissected, photographed, and further processed for histological observations.

Results: On histological observation of the brain, the cerebellum of the treated fetuses showed many pathological changes.

Conclusion: Aspirin, although widely used, may cause toxicity and teratogenicity. Clinicians, therefore, need to be cautious and judicious when prescribing aspirin to pregnant women, being aware of its potential embryo-fetal toxicity.

Key words: Cerebellum, Neurotoxicity, Teratogenicity

INTRODUCTION

Aspirin, is non-steroidal anti-inflammatory drug (NSAID) that is widely used to alleviate pain, reduce fever, and provide anti-inflammatory benefits.[1] It is frequently utilized by pregnant women, particularly during the initial stages of pregnancy. While NSAIDs are typically prescribed for chronic conditions such as inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy during pregnancy, aspirin also finds application in managing obstetric complications such as preterm labor and polyhydramnios. Surprisingly, it was only recognized for its preventive effects against heart attacks and ischemic strokes in the past 25 years, despite being used for over a century. The incidence of first-trimester exposure to aspirin can be attributed to women being unaware of their pregnancy. Studies conducted in Canada, Denmark, and Sweden reported a prevalence of early NSAID exposure during pregnancy of 2.9%, 3%, and 3.4%, respectively.[2-4] Aspirin is readily available over-the-counter, making it easily accessible without a prescription. The recommended safe dosage of aspirin ranges from 75 mg to 4 g per day. Its antithrombotic properties stem from the inhibition of the cyclooxygenase enzyme, which affects platelet function and reduces thromboembolic potential but may also lead to prolonged bleeding and bleeding complications.

Several studies have highlighted the vulnerability of the developing brain to various environmental insults, including exposure to medications during critical periods of gestation.[5-7] The cerebellum, a vital structure in the brain

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responsible for motor coordination and cognitive functions, undergoes dynamic development during the embryonic and early postnatal stages. Disruptions in cerebellar development can lead to long-lasting impairments in motor control and cognitive abilities.

The aim of this study is to investigate the potentially toxic effects of aspirin on the cerebellum of developing mice. We hypothesize that aspirin exposure during critical periods of cerebellar development may disrupt normal cellular processes, leading to structural and functional abnormalities in this brain region.

MATERIALS AND METHODS

Female Swiss albino mice weighing 20–25 g with an average age of 80–100 days were used in this study following approval from the institutional ethical committee. The mice were obtained from the Department of Anatomy, IMS, and BHU Varanasi Animal House.

Pregnant mice were divided into two groups as follows: Group 1: The control group administered an equivalent amount of tap water. Group 2: Treatment group orally administered aspirin at a dose of 100 mg/kg of body weight from day 3 to day 5 of gestation.

Each group consisted of 151 mice. Aspirin tablets (100 mg) from Reckitt Benckiser, Delhi, were used for the treatment. Prior to administration, one tablet was dissolved in 10 ml of tap water. The dosage of the drug was adjusted based on the body weight of the mice to achieve a proportionate dose of 100 mg/kg for the treated group. The drug was administered to the mice through oral gavage.

On the 19th day of gestation, mice from each group were euthanized using deep ether anesthesia. A uterotomy was performed to collect the fetuses. The general appearance and presence of gross malformations in the collected fetuses were documented through photography. Subsequently, the fetuses were preserved in a 10% neutral formalin solution for 7 days. After fixation, the fetal brains were dissected, photographed, and further processed for histological observations.

RESULTS

The control cerebellum shows well-defined three layers: the outer molecular, middle Purkinje, and inner granular layers [Figure 1]. In the treated cerebellum, there is thinning as well as loss of cohesion in the cells inside the molecular layer. The spaces between the different layers are also increased. The cellularity in each layer is also reduced considerably. The disappearance of cells and the cohesion of smaller vacuolated spaces give rise to the spongiform appearance of the treated cerebellar cortex [Figures 2 and 3].

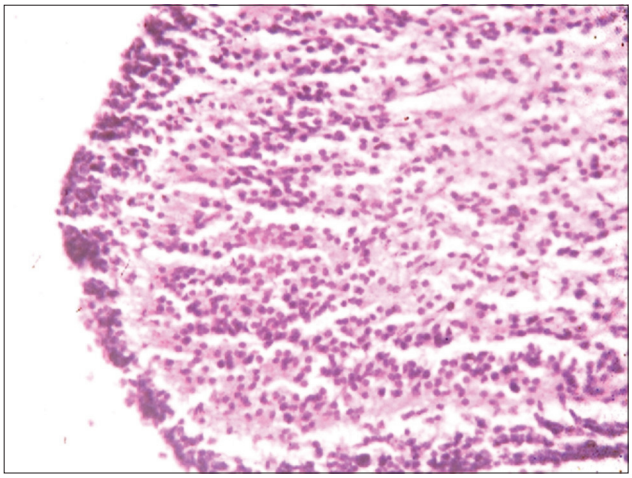

Figure 1: Photomicrograph showing control cerebellum (H and E, ×100)

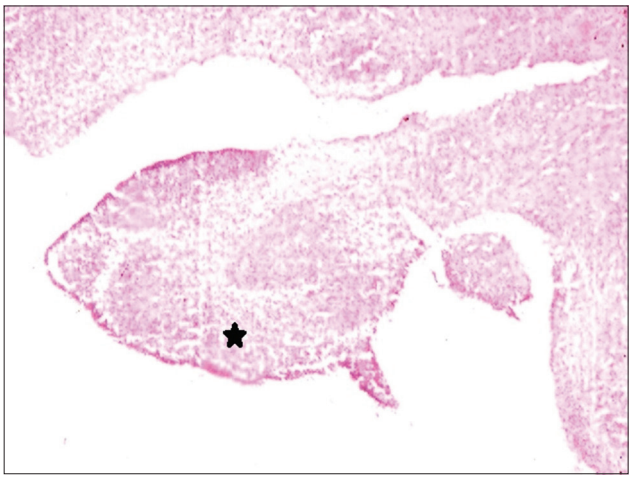

Figure 2: Photomicrograph showing treated Cerebellum (H and E, ×100). Showing reduced cellular density (★)

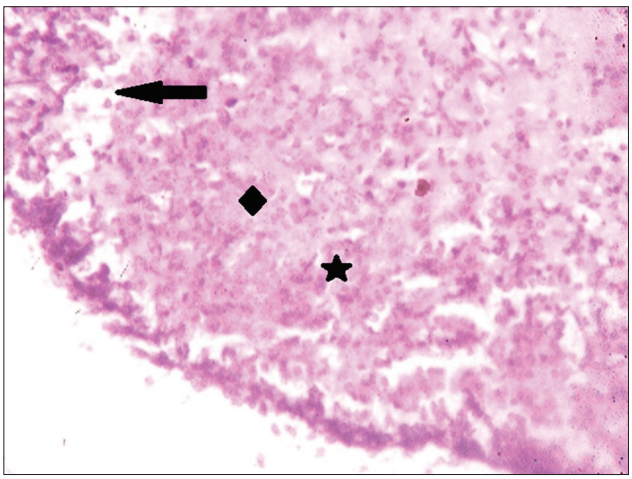

Figure 3: Photomicrograph showing treated cerebellum (H and E, ×400). Showing emptry spaces (→), degeneration of cells (★), paucity of cells (♦)

DISCUSSION

This study investigated the neurotoxic effects of aspirin on developing embryos. The findings of our study revealed significant evidence supporting the neurotoxic properties of aspirin during embryonic development.

The present study identified an increased incidence of apoptotic cell death in the brains of embryos exposed to aspirin. This suggests that aspirin may induce neurotoxicity by triggering apoptotic pathways, leading to the loss of developing neurons.

The observed neurotoxic effects of aspirin on the developing embryo align with previous studies that have reported similar findings.

In a study conducted by Sheppard *et al.*,[8] the focus was on investigating the negative effects of salicylate, the active component of aspirin, on various aspects of neurological health, such as hearing loss, neurotoxicity, tinnitus, and neuropathophysiology. The researchers discovered that the harmful effects of acetylsalicylate were primarily attributed to the inhibition of serotonin-mediated GABA inhibition, which plays a crucial role in maintaining precise frequency tuning in the auditory system.

Deng *et al.*[9] explored the impact of salicylate, including high doses of aspirin, on spiral ganglion neurons. Their findings indicated that elevated levels of salicylate induced an apoptotic response in these neurons, leading to cell death. Furthermore, it was observed that salicylate increased the production of superoxide radicals in spiral ganglion cells, suggesting a potential mechanism underlying the death of cochlear spiral ganglion neurons.

A recent meta-analysis[10] provided further evidence regarding the risks associated with maternal prenatal exposure to NSAIDs, including aspirin. The analysis indicated an increased risk of cerebral palsy and cognitive-behavioral disorders in offspring when mothers were exposed to NSAIDs or non-opioid painkillers during pregnancy. The interference with neurulation, the early process of brain development, was proposed as a potential mechanism contributing to the elevated risk.

Petersen *et al.*[11] conducted a study involving mother–child pairs from large cohorts in Denmark and Norway. Their findings revealed a significant association between aspirin use during pregnancy and a higher risk of bilateral spastic cerebral palsy in children.

In addition, on-going research by Landman *et al.*[12] aims to assess the long-term effects of antenatal exposure to low-dose aspirin compared to a placebo. The study focuses on evaluating survival rates, neurodevelopmental outcomes, behavioral patterns, and general health in children at the age of four. The primary focus is on identifying potential delays in neurodevelopment and the presence of behavioral problems, providing further insight into the possible neurotoxic effects of aspirin.

Collectively, these studies, along with our own findings, reinforce the notion of the neurotoxicity associated with aspirin exposure, shedding light on potential mechanisms and supporting the need for caution and further investigation when considering the use of aspirin during pregnancy.

CONCLUSION

The timing of aspirin administration during pregnancy plays a crucial role in influencing fetal development. Research has shown that when aspirin is given during early gestation, it is associated with an increased risk of miscarriage and congenital anomalies. Conversely, when administered during the third trimester of gestation, it has been linked to renal and vascular effects, including the closure of the ductus arteriosus and persistent pulmonary hypertension in newborns. It has been established that NSAIDs, including aspirin, can cross the placenta and reach the fetal circulation.

The primary pharmacological effect of aspirin on the developing fetus is believed to be through the inhibition of prostaglandin synthesis. This mechanism may contribute to the observed adverse effects on fetal development.

Given the growing use of low-dose aspirin as a prophylactic measure during pregnancy, it is essential to gather more long-term data to determine any potential harm and assess possible benefits in the future. Physicians need to be cautious and judicious when prescribing aspirin to pregnant women, being aware of its potential embryo-fetal toxicity. Close monitoring and individualized risk–benefit assessments are necessary to ensure the safety and well-being of both the mother and the developing fetus.

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