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Prophylactic Effect of Minocycline on Prevention of Preterm Brain Injury-Rat Model

Tamanna Kaur[1], Mrs.S.Sangeetha[2]
[1,2]Department of Anatomy, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical sciences (SIMATS), Saveetha University, Chennai - 600077, India.

Corresponding author email: sangeethas.sdc@saveetha.com

ABSTRACT

Introduction: *Preterm birth significantly risks brain development, leading to long-term neurological deficits such as cerebral palsy and learning disabilities. Current treatments for preterm brain injury are limited, necessitating new strategies. Minocycline, a second-generation tetracycline antibiotic, shows promise in adult neurological models for its anti-inflammatory and neuroprotective properties. This study investigates minocycline's prophylactic effects on preventing preterm brain injury using Wistar rat models, aiming to inform new clinical approaches for managing preterm brain injury in neonates.*

Materials and Methods:*After approval, pups were split into three groups: test, negative control, and positive control. On days 2, 4, and 6, rat pups received intraperitoneal injections of LPS (15 mg/kg) to induce preterm brain injury. The positive control group received normal saline, while the test group received minocycline (45 mg/kg) four hours before each LPS injection. Neurodevelopmental reflexes were performed for anomalies. Pups were euthanized at Postnatal day 15 for histopathology and immunohistology brain analysis.*

Results: *: The results suggest that minocycline treatment may improve neurodevelopmental outcomes in preterm rats, as indicated by quicker performance in various developmental tests compared to control groups. Histopathology reveals a decrease in ventricular dilatation compared to the negative group, implying that minocycline acts as a protective agent against preterm brain injury and effectively mitigates brain damage.*

Keywords: *Minocycline, prophylaxis, preterm brain injury, neuroprotection, rat model, inflammation, oxidative stress, neurodevelopment*

INTRODUCTION

Throughout the important developmental stage that occurs during neonatal intensive care from birth to term age, the preterm brain is susceptible to damage. A high risk of brain damage and deviation from the typical third-trimester trajectory of intrauterine brain maturation, involving both grey and white matter, are associated with preterm birth.(1)The preterm brain is vulnerable to damage throughout the critical developmental period that takes place in neonatal intensive care from birth to term age. Preterm birth is linked to a high risk of brain injury as well as a departure from the normal third-trimester trajectory of intrauterine brain maturation, involving both gray and white matter.(2)From a clinical and radiologic standpoint, neonatal brain damage can be difficult to identify due to the intricate interaction of maternal and perinatal variables. Different forms of brain injury may occur, depending on the infant's age and the degree of the insult(3).

The World Health Organization lists preterm birth, which is defined as a birth before 37 weeks of gestation, as one of the main health issues. It affects 5–7% of live newborns in the majority of affluent nations, and the problems that follow account for roughly 35% of neonatal fatalities worldwide as well as significant morbidity in survivors. Preterm birth is the cause of cerebral palsy in about 25% of instances. Numerous factors, such as prenatal asphyxia, infection or inflammation, prolonged hypoxia, and exposure to medications like corticosteroids and mechanical ventilation, might affect the development of brain injury in premature infants. There are presently very few choices for treatment(4).Preterm delivery can result in epilepsy, psychological illnesses, learning, memory, executive function, visual, and hearing abnormalities, as well as cerebral palsy or milder developmental coordination deficit.(5)

An albino outbred breed known as the wistar rat originated as the first "standardised" rodent used in cell biology and clinical medicine research. The Wistar rat is the basis for several rodent models, including the Lewis rat and the spontaneously hypertensive rat(6).With a lifespan of two to three years, albino wistar rats are distinguished by their pink complexion, white coat, red eyes, and long tail that makes up 85% of their body length. They have a gestation period of approximately 21-23 days and a typical litter size ranging

from 6 to 12 pups(7). In adulthood, every day of the animal is approximately equivalent to 34.8 human days.Albino In studies on neurobiology, wistar rats and humans are significantly comparable, especially in terms of brain structure and function. Their similarity to human brain areas in the hippocampus and cortex facilitates research on memory and learning. The similarity of neurotransmitter systems such as serotonin and dopamine facilitates study on psychiatric illnesses. The cognitive and behavioural processes of wistar rats are comparable, which makes them perfect for researching disorders including addiction, depression, and anxiety. Their ageing and developmental processes also shed light on neurodegenerative and neurodevelopmental disorders(8). The cognitive effects of hypoxia therapy were also investigated in albino wistar rats, which demonstrated increased memory retrieval, decreased anxiety, and improved mobility(9)(10,11).

In animal models, minocycline has demonstrated promise in reducing the severity of a range of neurological illnesses(10).The reason for its superior efficacy over doxycycline and tetracycline may be its increased ability to cross the blood-brain barrier.The efficaciousness of minocycline in neurological disorders is ascribed to its capacity to impede several pathways that result in harm, such as neuroinflammation and apoptosis.(12).Minocycline is a prospective treatment option for bacterial infections, cancer, autoimmune disorders, ischemia, neurological and mental diseases, since studies have demonstrated its multifaceted impacts on cell activities.(13)

Neuroprotective effects of minocycline, a semisynthetic tetracycline, have been demonstrated in several adult models of neurodegenerative illness and ischemia injury/stroke. Ongoing research is being done, nevertheless, to see whether minocycline has any neuroprotective effects on neonatal brain injury. Here we now show that in a mouse model of newborn hypoxic-ischemic brain injury, minocycline given either right before or right after a hypoxic-ischemic insult significantly lowers tissue damage.(14)

A tetracycline antibiotic renowned for its ability to reduce inflammation and inhibit microglial activation is minocycline.A number of brain illnesses, including ischemic brain damage, traumatic brain injury, brain haemorrhage , Parkinson's disease model, and Alzheimer's disease model, have been linked to protective benefits of minocycline.Furthermore, researchers show that minocycline can lessen the effects of inflammation on the brain in systemic inflammatory models. (15)

Minocycline is a tetracycline of the second generation that may be used as a neuroprotective treatment after brain damage. The clinical use of minocycline in neonates is controversial, despite the drug's well-established positive effects in a wide range of adult disease conditions. Neonates are not often given tetracyclines as a class, yet there is strong evidence that minocycline lessens brain damage following neonatal hypoxic-ischemic brain injury.(16)In various adult ischemia injury/stroke and neurodegenerative disease models, minocycline—a semisynthetic tetracycline—has been demonstrated to have neuroprotective effects. Nevertheless, the neuroprotective effects of minocycline following brain injuries to neonates have not been evaluated. We now show that in a mouse model of neonatal hypoxic-ischemic brain injury, minocycline given either immediately before or immediately after a hypoxic-ischemic insult significantly prevents tissue damage.(17)

Minocycline has direct anti-inflammatory properties since it can enter brain tissue.The aim of this project is to study the prophylactic action of minocycline on prevention of preterm brain injury on rat models.

METHODS AND MATERIALS

Animals and treatment

The approval for this project is given by Saveetha Dental College. Approval no. BRULAC/SDCH/SIMATS/IAEC/04-2024/05. Animals were transported in an air-conditioned vehicle with proper food and drinking water facility avoiding direct sunlight and heavy noise exposure with utmost care and periodic monitoring during travel period. These rats were housed for a period of 70 days.

To generate Preterm brain injury

To induce preterm brain injury , normally delivered rat pups will receive intraperitoneal injections of lipopolysaccharide (LPS, 15 mg/kg) on postnatal days 2, 4, and 6. This protocol aims to model neuroinflammation and assess the impact on brain development.

Prophylactic test group

For the prophylactic test group, the drug will be administered 4 hours prior to the LPS injection. This timing aims to evaluate the drug's effectiveness in preventing inflammation and subsequent brain injury in the rat pups.

Control test group

Negative Control pups will receive equal amounts of normal saline intraperitoneally on the same schedule. This group will serve as a baseline to compare the effects of LPS and the prophylactic drug on brain injury. Positive control groups consists of rats without LPS or Minocyclyne.

GROUP	Details	No.of Animals (pups)
1	Negative control(normal pups)	12
2	Disease control (LPS)	6
3	Treatment control(Minocyclyne)	6
4	Test group(Minocyclyne+LPS)	12

Table 1: Group details and the number of animals in each group. The groups are divided as follows: Normal control, Disease control (LPS), Treatment control (melatonin), and Test group (Melatonin + LPS).

Neurodevelopmental reflex testing

Pups will be assessed using neurodevelopmental reflex testing in a series of behavioural tests starting of various days including the Forelimb grasp test (PN Day 3),hind limb grasp test(PN Day 3), righting test(PN Day 3), hind limb placing test(PN Day 4), cliff avoidance test (PN Day 4),gait test(PN Day 6) ,auditory startle test (PN Day 10), posture test and eye opening test(PN Day 12) .These assessments aim to identify any neurodevelopmental and behavioural abnormalities resulting from the treatments. The combination of reflex and behavioural testing provides a comprehensive evaluation of the impact of E. coli, LPS, and prophylactic drugs on the pups' neurodevelopment and behaviour , allowing researchers to discern differences between treated and control groups and evaluate the effectiveness of the prophylactic intervention.

Post Natal day of starting test	Test
3	Forelimb Grasping
3	Hind limb Grasping
3	Righting
4	Hind limb placing
4	Cliff Avoidance
6	Gait
10	Auditory startle
12	Posture
12	Eye Opening

Table 2 : The Neurodevelopment tests performed with the Postnatal days they were performed on.


Image 1 Forelimb grasp test


Image 2 Forelimb grasp test


Image 3 Hindlimb grasp test


Image 4 Righting reflex test


Image 5 Righting reflex test


Image 6 Gait test


Image 7 Cliff avoidance **test**


Image 8 Cliff Avoidance test


Image 9 Eye opening


Image 10 posture test


Image 11 Rat pups


Image 12 Rat pups

Euthanization and Analysis

At the age of 15 and 35 days, the pups will be euthanized using carbon monoxide gas inhalation in a CO chamber after sedation with a suitable anaesthetic agent. Brain will be collected for subsequent analyses, including immunohistochemistry, ELISA, qPCR, Western blot, and other relevant tests. These procedures will help assess the molecular and cellular impacts of the treatments on various organs, providing comprehensive insights into the biological effects of E. coli, LPS, and the prophylactic drug. This approach aims to elucidate the mechanisms underlying preterm brain injury and potential protective interventions.

RESULTS

Neurodevelopmental tests

Groups	Forelimb Grasping	Hindlimb Grasping	Righting	Handlimb placing	Cliff avoidance	Gait	Auditory startle	Posture	Eye opening
Negative control (Dam 1)	5	6	6	6	6	9	10	12	15
Negative control (Dam 2)	5	6	5	6	5	8	11	13	16
Disease control	8	9	4	10	5	7	13	17	15
Treatment control	4	6	5	5	6	10	11	13	16
Test group (Dam 1)	4	4	4	4	5	9	10	13	16
Test group (Dam 2)	4	6	5	6	6	10	11	13	16

Table 3: Based on the grading of the neurodevelopmental tests for the negative control groups, Disease control group, Treatment control group and Test groups this table shows the maximum developmental activity attained throughout the postnatal days of the pups.

Histopathology of Brain

Image 13: Rat Brain

Image 14: Negative group-Photomicrograph of Brain section showing mild Ventricular dilatation

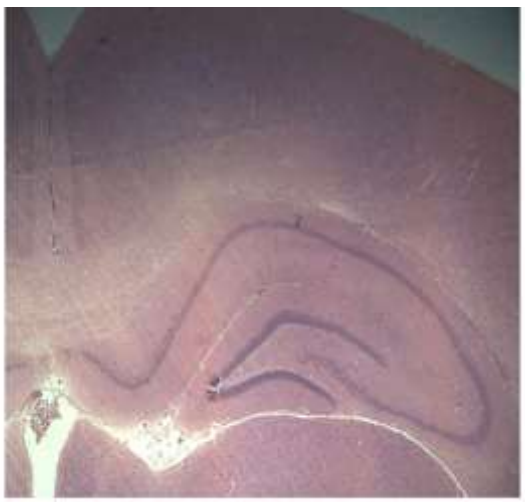

Image 15 : Positive control-Photomicrograph Of Brain section showing normal histoarchitecture of hippocampus and

cerebral cortex

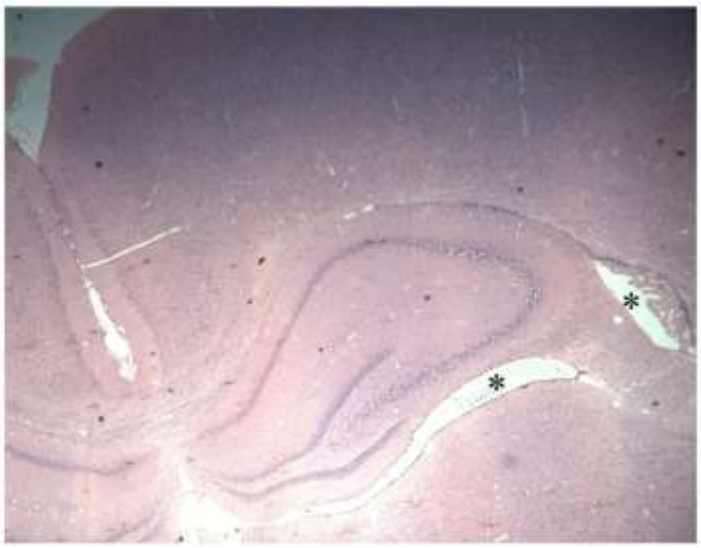

Image 16 : Test group-Photomicrograph of Brain section (H&E,X100) showing minimal Ventricular dilatation

DISCUSSION

1. **Forelimb Grasping:** This test evaluates motor strength and coordination. Disease control pups (LPS group) exhibited weaker forelimb grasping, indicating motor deficits due to preterm brain injury. Minocycline-treated groups (both treatment and test groups) showed improvement in grasping ability, suggesting that Minocycline helped preserve motor function.
2. **Hindlimb Grasping:** Similar to forelimb grasping, hindlimb grasping assesses motor coordination and strength. The disease control group had impaired hindlimb grasping, but treatment with Minocycline in the test groups (Dam 1 and Dam 2) led to better performance, indicating a protective effect of Minocycline on motor neuron integrity.
3. **Righting Reflex:** The righting reflex is an indicator of neurodevelopment and coordination. Pups in the disease control group were delayed in righting themselves, a sign of neurodevelopmental impairment. Minocycline-treated groups showed quicker righting times, demonstrating enhanced neurodevelopmental outcomes due to the treatment.
4. **Hand Limb Placing:** This test measures sensorimotor integration, where the ability of the rats to place their limbs accurately is tested. The disease control group displayed deficits in limb placing, likely due to neurological damage caused by inflammation from LPS exposure. Minocycline treatment improved limb placing, reflecting better sensorimotor function.
5. **Cliff Avoidance:** Cliff avoidance is a basic survival reflex that tests the animal's ability to sense and avoid danger. The disease control group had lower scores in cliff avoidance, suggesting compromised sensory and reflex pathways. In contrast, the Minocycline-treated groups demonstrated a better response, indicating preserved or restored reflexive behavior.
6. **Gait:** Gait analysis assesses motor coordination and balance. Rats in the disease control group showed abnormal gait patterns, indicating motor deficits. The treatment and test groups showed normalized gait patterns after Minocycline treatment, highlighting the drug's neuroprotective effect in preventing motor dysfunction.
7. **Auditory Startle:** This test assesses the auditory reflex and overall sensory function. The disease control group exhibited diminished startle responses, a possible result of brain injury. Minocycline-treated rats responded with stronger auditory startle reflexes, suggesting that the drug helped preserve sensory processing functions.
8. **Posture:** Proper posture is indicative of motor control and muscular coordination. The disease control group displayed abnormal postures, while Minocycline-treated groups had improved postural control, likely due to the drug's ability to prevent motor neuron damage and neuroinflammation.
9. **Eye Opening:** Eye opening is a developmental milestone in rodents. Delayed eye opening in the disease control group indicated delayed neurological development. However, both the treatment and test groups treated with Minocycline showed eye-opening times comparable to the negative control groups,

suggesting that Minocycline supports normal neurodevelopment even under conditions of preterm brain injury.

A study on the prophylactic effect of Minocycline in preventing preterm brain injury in a rat model indicates that the Test group (Dam 1), which received Minocycline before LPS, exhibited the highest level of neurodevelopment. This was evidenced by the fastest outcomes across most neurodevelopmental measures, including forelimb and hindlimb grasping, righting, hindlimb placing, cliff avoidance, gait, auditory startle, and posture. The Treatment control group (Dam 2) which received only minocycline and Negative control groups (Dam 1 and Dam 2) that consisted of normal rat pups demonstrated moderate neurodevelopment, with results manifesting on later postnatal days compared to the Test group (Dam 1) but earlier than the Disease control group. The Disease control group , which did not receive Minocycline and only LPS, showed the lowest neurodevelopment, with delayed outcomes particularly in hindlimb placing, gait, auditory startle, and posture. Overall, the data suggest that Minocycline significantly improves neurodevelopment and can effectively prevent preterm brain injury, as evidenced by the accelerated development in the Test group (Dam 1) compared to the other groups.(18).The hippocampal region is studied in connection to preterm brain injury because it is a crucial region for cognitive functions such as memory formation and spatial orientation(19). Due to their brains' immature state, preterm newborns are more susceptible to brain traumas, which frequently impact the hippocampal region(20). Long-term cognitive problems and neurological abnormalities may result from damage to this region.The histopathological analysis of rat brain sections in this study evaluates the prophylactic effect of minocycline on preterm brain injury(21). The negative control group, shown in Image 1, displays mild ventricular dilatation, indicating some degree of brain injury. In contrast, the positive control group in Image 2 exhibits normal histoarchitecture of the hippocampus and cerebral cortex, serving as a benchmark for healthy brain tissue.This group's brain structure serves as a crucial reference point, illustrating what a healthy, undamaged brain should look like. Notably, Image 3 illustrates the test group that received minocycline treatment and shows very little dilation of the ventricles. This decrease in ventricular dilatation in comparison to the negative group implies that minocycline is a protective agent against preterm brain injury and effectively mitigates brain injury.The comparison across groups highlights minocycline's potential to safeguard the developing brain against the adverse effects of premature birth, making it a valuable therapeutic strategy for improving outcomes in preterm infants.Due to their critical roles in cognitive processes including as memory formation, higher-order processing, and spatial navigation, the hippocampus and cerebral cortex are investigated in relation to premature brain injury. (22).While the cerebral cortex is necessary for cognitive functions, motor control, and sensory perception, the hippocampus is involved in memory and learning(23) .The neuroprotective and anti-inflammatory properties of Minocycline, a second-generation tetracycline derivative, have garnered considerable interest in the context of CNS trauma and neurodegenerative diseases. Previous research has demonstrated its efficacy in various animal models, highlighting its potential to mitigate brain injury and improve long-term outcomes. (24)This discussion synthesises findings from recent studies on the prophylactic and therapeutic effects of Minocycline, especially in preterm brain injury, subarachnoid haemorrhage (SAH), traumatic brain injury (TBI), and other CNS conditions(25).In a mouse model of SAH, low-dose Minocycline has been shown to protect brain microvascular ultrastructures by preventing endothelial cell abnormalities and preserving blood-brain barrier (BBB) integrity. The neuroprotective mechanisms include defence against oxidative stress and immune cell infiltration in the perivascular region . These findings suggest that Minocycline could be a promising therapeutic agent for reducing the effects of SAH-induced brain injury, highlighting its ability to protect microvascular structures and prevent harmful ultrastructural changes(26). Minocycline has demonstrated significant neuroprotective effects in TBI models. Administered 24 hours post-injury, Minocycline reduced microglial activation, monocyte infiltration, and hippocampal neuronal loss within a week. Long-term benefits included reduced hippocampal neurodegeneration, preserved white matter, and improved memory at six months. The timing and duration of treatment were crucial, underscoring the importance of the therapeutic window in TBI management . These results suggest that Minocycline could be an effective therapeutic option for TBI, particularly if administered within an optimal time frame(27). Minocycline has shown efficacy in various animal models of acute CNS injury and chronic neurodegeneration, including spinal cord damage, intracerebral haemorrhage, and ischemic stroke . Its neuroprotective properties are primarily attributed to its anti-inflammatory and anti-apoptotic effects, often mediated through the inhibition of the p38 MAPK pathway(25) . This pathway is a key regulator of immune function and

apoptosis, and targeting it can reduce neural inflammation and prevent cell death. However, it is important to note that Minocycline has shown limited efficacy in models of Huntington's, Parkinson's, and hypoxia-ischemia (28).

Other therapeutic agents have also shown promise in reducing brain injury and improving outcomes in various models. For example, Grifolin has demonstrated neuroprotective effects in acute cerebral ischemia by inhibiting apoptosis and reducing inflammation (29). Hyperbaric oxygen therapy has been effective in mitigating brain injury in juvenile rats exposed to repeated mild impacts, suggesting potential benefits for adolescent athletes at risk of concussions(30) . Additionally, maternal administration of melatonin has been shown to reduce inflammation, preterm birth, and perinatal brain injury, highlighting its potential as a therapeutic intervention in cases of maternal inflammation(31) .

Future Scope

In order to further investigate the preventive role of minocycline in averting preterm brain damage, the following crucial research avenues ought to be explored.First and foremost, human trials are necessary to evaluate the safety and efficacy of minocycline in preterm newborns and to ascertain whether or not it might be used as a regular medication to prevent neurological deficits. Second, in order to maximise benefits and minimise negative effects, optimal dosage and time for administration must be determined through optimal dosing studies.

Long-term Outcomes research will determine whether minocycline treatment is viable as a long-term intervention by assessing the treatment's long-term effects on neurodevelopment and general health. Mechanistic studies should investigate the cellular and molecular mechanisms that underlie minocycline's neuroprotective benefits, clarifying how it averts brain damage and fosters development. It's also critical to look for combination therapies because mixing minocycline with other neuroprotective drugs may improve treatment outcomes and offer a more comprehensive defensive approach. Finally, research on Broader Applications aims to evaluate the effectiveness of minocycline in different models of neonatal brain injury and associated disorders, ascertaining its suitability for a broader spectrum of neurological ailments impacting infants.

Limitations

Several key difficulties need to be overcome before the research on minocycline's potential as a preventive measure against preterm brain injury can proceed. First and foremost, findings derived from animal models such as rats,need to be thoroughly verified for application to humans via species-specific research. To confirm the safety and efficacy of minocycline in preterm neonates while accounting for any pertinent physiological abnormalities, these trials are crucial.Finding the right dosage and timing for minocycline administration is crucial, too. This means minimizing any side effects while weighing the benefits of treatment, particularly in newborns who are vulnerable to pharmacological treatments. Extensive safety evaluations are required to ensure that the therapy does not compromise the newborn's health.

Last but not least, understanding the complexity of preterm brain injury highlights the necessity of careful study. Although animal models might provide insightful information, they may not fully capture the complexity of human settings. Improving our understanding of these complexities will improve treatment strategies and lessen the effects on premature infants who are vulnerable to neurodevelopmental delays.

CONCLUSION

The study demonstrates that Minocycline significantly enhances neurodevelopment and protects against preterm brain injury in a rat model. Rats treated with Minocycline before LPS exposure showed the fastest neurodevelopmental improvements across several measures, including forelimb and hindlimb grasping, righting, hindlimb placing, cliff avoidance, gait, auditory startle, and posture, compared to other groups. The Treatment control group and the Negative control groups exhibited moderate neurodevelopment, with results appearing later than the Test group but earlier than the Disease control group, which showed the most delayed outcomes. Histopathological analysis further supports these findings, revealing that Minocycline-treated rats exhibited minimal ventricular dilatation, indicating reduced brain injury, in contrast to the Negative control group that showed mild ventricular dilatation. These findings suggest that Minocycline is a promising prophylactic agent for preventing preterm brain injury, highlighting its potential to mitigate brain injury and improve neurodevelopmental outcomes in preterm infants.

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