Cilostazol, a Type III Phosphodiesterase Inhibitor, Reduces Ischemia/Reperfusion-Induced Spinal Cord Injury

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ABSTRACT

Background: Spinal cord injury is still a devastating complication after surgical repair of thoracoabdominal aortic pathologies. In this study, we investigated the protective effect of cilostazol, a type III phosphodiesterase inhibitor, against ischemia/reperfusion (I/R)-induced spinal cord injury in rats.

Methods: Twenty-four rats were assigned to 3 experimental study groups: the control group (sham operation, n = 8); the ischemia group (nontreated, n = 8), which underwent aortic occlusion without pharmacologic intervention; and the cilostazol-treated group (n = 8), which received 20 mg/kg cilostazol per day orally for 3 days before spinal ischemia. All animals underwent a 45-minute period of spinal cord ischemia via clamping of the abdominal aorta between the left renal artery and the aortic bifurcation; removal of the aortic clamp was followed by reperfusion. Neurologic status was assessed before spinal ischemia and at 48 hours after the operation. All animals were sacrificed at 48 hours after the operation. Spinal cords were harvested for histopathologic examination and biochemical analyses for the malondialdehyde (MDA) level and superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities.

Results: Tarlov scores at postoperative hour 48 tended to be higher in the cilostazol-treated group than in the nontreated ischemia group (mean ± SD, 3.66 ± 0.40 versus 2.32 ± 0.80; P = .08). Spinal cord tissue MDA levels (per gram protein) were lower in the cilostazol-treated group than in the nontreated ischemia group (0.27 ± 0.01 mmol/g versus 0.33 ± 0.04 mmol/g, P = .026), and the cilostazol-treated group had higher activities of tissue SOD (519.6 ± 56.3 U/g versus 438.9 ± 67.4 U/g, P = .016) and GSH-Px (4.07 ± 1.37 U/g versus 3.21 ± 1.02 U/g, P = .47) than the nontreated ischemia group. Histopathologic analyses demonstrated that cilostazol treatment attenuated I/R-induced cellular damage.

Conclusion: Administration of cilostazol before spinal cord ischemia reduced neurologic injury and produced clinical improvement by attenuating oxidative stress in this rat spinal cord I/R model.

INTRODUCTION

Neurologic complications remain one of the most devastating types of complications after surgery for thoracoabdominal aneurysms (incidence, 2.9%-32%) [Wada 2001]. Inadequate blood supply, hypoxic endothelial cell activation, leukocyte–endothelial cell interactions, and neutrophil-mediated injury are the potential predisposing factors for spinal cord injury, which may lead to paraplegia after surgery [Boyle 1995; Wada 2001]. The dissemination of aortic pathology, the duration of aortic clamping, and the level of ischemia affect the postoperative outcomes of patients despite recent advances in operative techniques, anesthesia management, and postoperative care [Coselli 1997]. Neutrophil activation and oxidative stress have been studied with regard to the pathogenesis of spinal cord ischemia/reperfusion (I/R) injury [Ueno 1994; Boyle 1996], and these factors have been closely associated with production of oxygen free radicals, lipid peroxidation, protein damage, and DNA damage. Consequently, protection of the spinal cord from I/R injury can be achieved by decreasing oxidative stress.

Cilostazol, an antiplatelet drug used to treat intermittent claudication, increases the intracellular level of cyclic adenosine monophosphate (cAMP) by inhibiting its hydrolysis by type III phosphodiesterase. Its cardiovascular effects include inhibition of platelet aggregation, antithrombosis, and vasodilatation via an increased cAMP level [Kimura 1985; Tanaka 1989; Kohda 1999]. Recently, the neuroprotective effects of cilostazol against focal cerebral ischemic injury have been found in experimental studies with rats [Choi 2002; Lee 2003; Watanabe 2006; Manickavasagam 2007]. This neuroprotective potential has been ascribed to its anti-inflammatory and antiapoptotic effects mediated by scavenging of hydroxyl radicals; however, the effects of cilostazol on spinal cord I/R injury have not been reported to date.

This study was designed to investigate the protective efficacy of cilostazol on the neurologic and histopathologic outcomes of rat spinal cord ischemia produced by aortic occlusion.
MATERIALS AND METHODS

Study Design
After approval of the study by the local institutional committee, experiments were performed on 24 male Wistar albino rats between 260 and 380 g (mean ± SD, 295 ± 21.5 g). All rats received humane care in compliance with the European Convention on Animal Care. The animals were kept within the same unit at a room temperature between 18°C and 21°C. Feeding of the animals was made by the same nutrition protocol with a standard rat chow (Bil-Yem Gida Sanayi Tic, Yenikent, Ankara, Turkey). The animals were followed for 15 days before the procedure. All rats were neurologically intact before anesthesia and surgical manipulations.

All animals received premédication with atropine sulfate (0.005 mg/kg subcutaneously). Rats did not receive food or water within 8 hours before anesthesia. They were anesthetized by intramuscular injection of ketamine hydrochloride (0.005 mg/kg subcutaneously). Rats did not receive food or water within 8 hours before anesthesia. They were anesthetized by intramuscular injection of ketamine hydrochloride (40 mg/kg) and xylazine (10 mg/kg). Anesthesia was maintained by intermittent delivery of ketamine (25 mg/kg) without endotracheal intubation and mechanical ventilation. The animals received oxygen at 200 mL/minute via a pediatric face mask throughout the procedure. A 24G catheter was surgically inserted into the left internal jugular vein to provide intravenous fluid replacement (0.9% isotonic saline solution). The same surgical area was used to cannulate the left carotid artery for monitoring the proximal blood pressure after aortic clamping. The core temperature above 36°C was followed with a rectal probe. Each procedure was performed in the same operating room at ambient temperature. The animals received prophylactic antibiotics (procaine penicillin, 200,000 units administered intramuscularly twice a day) for 2 days in the immediate postoperative period.

Experimental Groups and Surgical Procedure
In this experimental study, animals were divided into 3 groups in a randomized fashion. The vehicle-treated sham-operation group (n = 8) underwent operation in the same fashion as the other 2 groups but without aortic occlusion and drug intake. The animals in the vehicle-treated ischemia group (n = 8) underwent aortic clamping and spinal cord ischemia for 45 minutes without drug intake. The cilostazol group (n = 8) received cilostazol therapy (20 mg/kg per day orally) for 3 days before the operation; aortic clamping and spinal cord ischemia were performed for 45 minutes.

Animals in the cilostazol group were pretreated with cilostazol by gavage (20 mg/kg orally daily) for 3 days before induction of ischemia [Manickavasagam 2007]. Cilostazol was dissolved in dimethyl sulfoxide (30%) immediately before use and administered within a half hour. All groups received reperfusion after spinal cord ischemia. Vehicle-treated rats received 1 mL of 30% dimethyl sulfoxide solution orally.

After a standard midline laparotomy incision, the abdominal aorta was explored via a transperitoneal approach by retracting the intestines. The aorta between the renal arteries and the aortic bifurcation was exposed for clamping. Heparin sodium (150 U/kg) was administered intravenously before aortic cross-clamping. The abdominal aorta was clamped at 2 sites: just distal to the left renal artery and proximal to the aortic bifurcation. During aortic clamping, the arterial blood pressure was monitored from the left carotid artery catheter (24G). This catheter was connected to a blood pressure/heart rate transducer and monitor (Hewlett-Packard 1495C; Hewlett-Packard, Palo Alto, CA, USA). In the event of lability, fluid was replaced through the central venous catheter. The clamps were removed after 45 minutes of spinal cord ischemia, thereby allowing reperfusion. The abdominal wall was closed in a double-layer fashion with 4-0 Prolene suture.

Postoperative analgesia was provided by subcutaneous injection of bupivacaine hydrochloride (0.25%). Rats were separated from each other to allow optimal recovery from anesthesia. Sham-operated animals underwent the same operative conditions; however, aortic occlusion or drug intake was not performed.

Postoperative Care and Assessment of Neurologic Functions
At 1 hour of reperfusion, arterial and venous lines were removed, and all medications were stopped. The animals were returned to their cages after they awoke from the anesthesia. The Crede maneuver was used to empty the bladders of the paraplegic animals at least twice daily. No animal died in the postoperative period.

An independent observer who had been blinded to the study protocol evaluated the neurologic functions of the animals. All rats underwent a neurologic examination preoperatively and at 48 hours after surgery. This examination included an evaluation of motor and sensory function. Spinal cord function was graded according to the modified Tarlov scoring system [Tarlov 1972], as follows: grade 0, paraplegic with no movement; grade 1, poor lower-extremity motor function; grade 2, some lower-extremity motor function with good antigravity strength, sits with assistance; grade 3, sits alone; grade 4, weak hop; grade 5, normal motor function, hop.

Sacrificing of Animals and Sample Preparation
Immediately after functional assessment, the rats were sacrificed via a lethal intracardiac injection of pentobarbital (100 mg/kg). Sections of the lumbar spinal cord were harvested for histologic examination immediately after the lethal injection. The spinal cord between L1 and S1 was extracted carefully via an anterior approach. Each spinal cord was longitudinally divided into 2 equal parts with a fine scalpel. One of the halves was fixed in 10% neutral buffered formalin solution and embedded in paraffin. The other half was snap-frozen for histopathologic examination.

Measurement of Malondialdehyde Levels and Antioxidant Enzyme Activities
The frozen tissues were homogenized in phosphate buffer (pH 7.4) by means of a homogenizer (Heidolph Dix 900; Heidolph Elektro, Kelheim, Germany) on an ice cube. The supernatant was used for all assays. Initially, the protein content of tissue homogenates was measured by the method of Lowry et al, with bovine serum albumin as the standard [Lowry 1951].
Spinal cord tissue was studied spectrophotometrically with a method based on the reaction of the carbonyl group with 2,4-dinitrophenylhydrazine to form 2,4-dinitrophenylhydrazone. 2,4-Dinitrophenylhydrazine was the reagent originally used for proteins subjected to metal-catalyzed oxidation. Absorbances were measured with a spectrophotometer (Helios Epsilon; Unicam, Cambridge, UK). The results were expressed as millimoles carbonyl per gram protein.

The lipid peroxidation level was measured by the thiobarbituric acid reaction according to the method of Ohkawa et al [1979]. This method was used to obtain a spectrophotometric measurement of the color produced during the reaction of thiobarbituric acid with malondialdehyde (MDA) at 535 nm. MDA levels were expressed in millimoles per gram protein.

Superoxide dismutase (SOD) activity was assayed by the nitroblue tetrazolium (NBT) method of Sun et al [1988]. In this method, O$_2^-$ reduces NBT to blue formazan, which has a strong absorbance peak at 560 nm. One unit of SOD activity is defined as the amount of protein that inhibits the rate of NBT reduction by 50%. The estimated SOD activity was expressed in enzyme units per gram protein.

Glutathione peroxidase (GSH-Px) activity was measured by the method of Paglia and Valentine [1967], in which GSH-Px activity is coupled with the oxidation of NADPH by glutathione reductase. NADPH oxidation was followed spectrophotometrically at 340 nm at 37°C. The absorbance at 340 nm was recorded for 5 minutes. GSH-Px activity, measured as the slope of the line, was expressed in millimoles NADPH oxidized per minute. GSH-Px activity was presented as enzyme units per gram protein.

**Histologic Examination**

The paraffin-embedded spinal cord samples were sectioned into 4-μm-thick transverse sections, which were then stained with hematoxylin and eosin. Two observers who were blinded to the groups examined the sections by light microscopy to assess the degree of spinal cord injury. The gray matter (motor neurons) and white matter (axonal structure and glial cells) were assessed for ischemic injury. Ischemic injury scores in each sample were estimated as previously described [Güler 2010]. A semiquantitative scale was devised to evaluate ischemic features. Five spinal cord injury parameters were evaluated: motor neurons with shrunken cellular bodies, an intensely eosinophilic cytoplasm, triangular and pyknotic nuclei, hemorrhage, and axonal vacuole formation. At least 10 fields from each spinal cord section were examined for the severity of these changes. Spinal cord injury was scaled relatively as 0, 1, 2, and 3 for absent, minimal, moderate, and severe injury, respectively. The mean score was calculated for each parameter, and the total histologic injury score was estimated for each group by adding the individual scores, for a maximum possible score of 15.

**Statistical Analysis**

Statistical analysis was performed with SPSS software (release 15.0 for Windows; SPSS, Chicago, IL, USA). All data are presented as the mean, SD, median, and range. The normality of the distributions of biochemical measurements at the end of the study was assessed both graphically and statistically.

![Figure 1. Mean (SD) Tarlov scores at postoperative hour 48 after reperfusion.](image-url)
with the Shapiro-Wilk test. The SOD and GSH-Px data were not consistent with a normal distribution. Whereas SOD and GSH-Px values were compared with the Kruskal-Wallis variance analysis test, MDA values for the groups were compared by one-way analysis of variance. The Bonferroni-adjusted Mann-Whitney U test was also used to compare the groups. A P value <.05 was considered statistically significant.

**RESULTS**

**Operative Parameters**

No complications developed during the surgical procedures. No differences in arterial pressures or body temperatures were observed before ischemia among the control groups and the cilostazol-treated group. Values for the parameters remained similar in each group during the procedures. The femoral artery blood pressure fell in the animals during ischemia and remained near zero. It gradually recovered to normal within the first few minutes of reperfusion.

**Evaluation of Neurologic Function**

All rats in the sham group had normal results in the neurologic examination; however, all rats in the ischemia group presented with severe neurologic deficits after surgery, including total paraplegia. These animals had a worse neurologic status than in the sham group (P < .05). The mean Tarlov score at postoperative hour 48 was higher in the cilostazol-treated group than in the ischemia group (Figure 1), a result implying an improved functional neurologic outcome associated with the use of cilostazol. The mean (±SD) Tarlov scores at 48 hours postoperatively in the ischemia and cilostazol-treated groups were 3.66 ± 0.40 and 2.32 ± 0.80, respectively (P = .08).

**Biochemical Parameters**

Table 1 summarizes the tissue distributions MDA, SOD, and GSH-Px levels in the 3 groups. The groups’ antioxidant and MDA levels were compared with the post hoc Mann-Whitney U test. The sham group was significantly different, compared with the ischemia and cilostazol groups. In particular, a significant difference was observed between the ischemia and cilostazol-treated groups.

MDA levels were lower in the cilostazol-treated group than in the ischemia group (0.27 ± 0.01 mmol/g versus 0.33 ± 0.04 mmol/g, P = .026; Figure 2). This finding indicated a decreased oxidative stress after cilostazol treatment. The highest MDA level was detected in the ischemia group, and the lowest measured value occurred in the sham group.

The cilostazol-treated group had a higher mean SOD activity level than the ischemia group (519.6 ± 56.3 U/g...
versus 438.9 ± 67.4 U/g, \( P = .016 \); Figure 3). The highest SOD level was observed in the sham group, and the lowest SOD activity level occurred in the ischemia group. These findings suggest an increased resistance to oxygen free radicals and oxidative stress after cilostazol pretreatment before spinal cord ischemia.

The level of GSH-Px activity was significantly higher in the cilostazol-treated group than in the ischemia group (4.07 ± 1.37 U/g versus 3.21 ± 1.02 U/g, \( P = .47 \); Figure 4). The highest GSH-Px level was detected in the sham group, and the lowest value occurred in the ischemia group.

**Histologic Examination**

The histologic results for the spinal cords from animals in the sham-treated group showed a normal structure for motor neurons, axons, and glial cells. In the ischemia group, the motor neurons cells in the gray matter showed necrotic and apoptotic enlargement, shrinkage, chromatin condensation, and nuclear budding. Enlargement of glial nuclei and axonal vacuoles were seen in the white matter. The ischemia plus cilostazol group showed marked reductions in necrotic neurons compared with the ischemia group. Most of the cells in neuron populations were preserved. Gial cells of the white matter were mostly protected in this group. Nevertheless, axonal structures in the white matter were mostly deteriorated compared with normal white matter (hematoxylin and eosin; scale bars, 40 µm).

![Figure 5. Representative light microscopy photographs of spinal cord sections. In the sham-treated group (A, B), sections of gray and white matter showed normal structure for motor neurons, axons, and glial cells. In the ischemia group (C, D), the motor neurons cells in the gray matter show necrotic and apoptotic enlargement, shrinkage, chromatin condensation, and nuclear budding. Enlargement of glial nuclei and axonal vacuoles were seen in the white matter. The ischemia plus cilostazol group (E, F) showed marked reductions in necrotic neurons compared with the ischemia group. Most of the cells in neuron populations were preserved. Gial cells of the white matter were mostly protected in this group. Nevertheless, axonal structures in the white matter were mostly deteriorated compared with normal white matter (hematoxylin and eosin; scale bars, 40 µm).](image)

### Table 2. Histologic Spinal Cord Injury Scores for Each Group*

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Scores of Spinal Cord Injury</th>
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</thead>
<tbody>
<tr>
<td>Control (n = 8)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>I/R only (n = 8)</td>
<td>9 (5-12)†</td>
</tr>
<tr>
<td>Cilostazol (n = 8)</td>
<td>5 (3-6)‡</td>
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</table>

*Histologic grading of injury is displayed as the median (range). I/R indicates ischemia/reperfusion.
†Significantly different from control (\( P < .05 \)).
‡Significantly different from the I/R group (\( P < .05 \)).

apoptotic cells that exhibited shrinkage, chromatin condensation, and nuclear budding. Necrotic neurons exhibited cellular swelling, cytoplasmic puffing, and pyknosis. Destruction of the entire white matter was observed, with marked enlargement of vacuoles and axonal swelling. The significantly increased total injury score in the I/R group indicated significant spinal cord injury. After cilostazol treatment, the damage to the motor neuron cells was only slight, and large populations of cells were preserved. Nevertheless, axonal structures in the white matter were mostly deteriorated compared with normal white matter (Figure 5). Conversely, the total histologic injury score was significantly decreased in the cilostazol-treated group, indicating significant attenuation of the spinal cord injury. Table 2 summarizes the histologic spinal cord injury scores.

**DISCUSSION**

Spinal cord injury after surgery of the descending and thoracoabdominal aorta is still a devastating complication and may lead to postoperative paraparesis or paraplegia. Neurologic complications can develop within 2 to 5 days after surgery. The incidence of spinal cord injury and associated neurologic complications is primarily related to the duration and severity of the ischemia, as well as to reperfusion injury [Ueno 1994; Wada 2001]. Therefore, different surgical strategies have been developed to reduce the incidence of spinal cord injury after aortic operations [Wada 2001; Coselli 2002; Bisleri 2005; Awad 2010].

The pathogenesis of neurologic complications after spinal cord ischemia includes oxidative stress due to the reperfusion of the aorta and tissues [Kirsch 1992; Ueno 1994]. Spinal cord injury after aortic surgery is associated with a metabolic burst in I/R injury at the intracellular level, in which oxygen is reduced to superoxide (\( O_2^- \)), hydrogen peroxide (\( H_2O_2 \)), and hydroxyl radical (\( OH^- \)) [Dickens 1988]. These oxygen radicals are generated by ischemia and reoxygenation of the energy-depleted cells. Reperfusion significantly increases the production of these radicals and contributes to tissue injury. Oxygen free radicals cause cellular death or apoptosis through endothelial damage, lipid peroxidation, and intracellular protein and DNA damage [Ueno 1994].

Antioxidant enzyme activities such as those of the SODs (CuZn-SOD and Mn-SOD), catalase activity, and enzymes and metabolites involved in the glutathione cycle (including reduced glutathione, oxidized glutathione, glutathione...
reductase, and GSH-Px) provide protection against cellular toxicity from oxygen free radicals after reperfusion. The absence or dysfunction of these scavengers makes the cell vulnerable to oxidative injury [Dobashi 2000]. SOD and GSH-Px are the most important intracellular antioxidants in humans, and studies relating to their activity levels have noted their roles in protecting against lipid peroxidation and tissue injury. The tissue MDA level is also indicative of oxidative stress that causes lipid peroxidation and cellular damage. Previous studies indicated that oxidative stress associated with I/R injury reduces SOD and GSH-Px activities and increases the MDA level as a product of lipid peroxidation [Dobashi 2000].

We therefore investigated the potentially protective properties of cilostazol, a type III phosphodiesterase inhibitor, which has recently been studied as an effective antioxidant agent with respect to its neuroprotective effects [Choi 2002; Lee 2003; Watanabe 2006]. In addition to its antioxidant effect, the neuroprotective potential of cilostazol has been ascribed to its anti-inflammatory properties. Cilostazol increases the levels of intracellular cAMP in endothelial cells and platelets, leading to dilatation of smooth muscle cells of the arterioles and inhibition of platelet aggregation [Kimura 1985]. In an experimental study, Takei et al [1998] demonstrated that increased AMP inhibits the production of H$_2$O$_2$ and superoxide anion radicals in alveolar macrophages after I/R injury. Cilostazol-stimulated increases in cAMP are one of the potential protective effects of this drug against I/R injury. Ota et al [2008] also indicated that cilostazol exerted protective effects against endothelial injury and dysfunction via an increase in protein kinase A and endothelial nitric oxide synthase activities. The authors suggested that nitric oxide production via cilostazol had a protective effect against oxidative stress. Recent studies have noted the neuroprotective effect of cilostazol against focal cerebral ischemia via its antiapoptotic action [Watanabe 2006]. Choi and colleagues demonstrated that cilostazol treatment decreased ischemic brain infarction in rats in association with inhibition of apoptotic and oxidative cell death [Choi 2002]. These authors noted a potent ability of cilostazol to scavenge hydroxyl and peroxyl radicals in in vitro experiments. Honda et al [2006] showed that cilostazol attenuated gray and white matter damage in rats at 24 hours after focal cerebral ischemia. Recently, Lee et al [2004] reported that cilostazol significantly suppressed the laddering feature of DNA fragmentation (a sign of oxidative stress) in rats for samples obtained at 24 and 48 hours of reperfusion after 2 hours of cerebral ischemia. Magnetic resonance imaging also demonstrated a reduction in brain ischemic infarction in rats [Lee 2003]. Additionally, in vitro and in vivo studies with different experimental animal models have demonstrated that cilostazol exerts highly significant neuroprotection because of its pleiotropic effects. Sekiguchi et al [2008] reported that cilostazol improved nerve conduction velocity and blood flow to the cauda equina in a dog model. The authors concluded that cilostazol is a potential agent for improving symptoms due to compression of the cauda equina and/or cauda equina dysfunction.

In this study, cilostazol decreased oxidative stress after spinal cord I/R injury with respect to the tissue levels of antioxidant agents. Spinal cord MDA levels (indicative of oxidative stress involving lipid peroxidation in spinal myelin) at 48 hours after aortic occlusion were significantly elevated in the ischemia group, implying the involvement of oxygen free radicals in neuronal injury. We observed, however, less of an increase in MDA content in the spinal cord after I/R when cilostazol was administered before aortic occlusion. Similarly, SOD and GSH-Px activity levels also increased significantly in the cilostazol-treated group, compared with the ischemia group. These data, which confirm the neuroprotective effects of cilostazol in spinal cord ischemia, suggest that the mechanism of this action may involve changes in the levels of antioxidant agents after spinal cord injury.

The results of the present study show that cilostazol administration prior to ischemia had a protective effect on rat spinal cord motor neurons. Histopathologic evaluations demonstrated that motor neurons in the gray matter of the nontreated group consisted of apoptotic cells that exhibited shrinkage, chromatin condensation, and nuclear budding. The number of motor neurons was significantly lower in this group than in the cilostazol-treated group. Additionally, the nontreated group had histologic evidence of the destruction of the entire white matter, with marked enlargement of vacuoles and axonal swelling. On the other hand, damage to the motor neuron cells was only slight in the cilostazol-treated group, and large populations of cells were preserved. Finally, the histopathlogic findings were correlated with the results of the neurologic functional assessment. The mean Tarlov score at 48 hours after surgery was significantly higher in the cilostazol-treated group than in the nontreated group, implying an improved neurologic function outcome.

In conclusion, cilostazol treatment before tissue ischemia protects the spinal cord from I/R injury in rats. This protection is probably associated with decreased oxidative stress in spinal cord tissue. We observed that cilostazol increases the activities of antioxidant enzymes, including SOD and GSH-Px, and decreases tissue MDA levels that indicate lipid peroxidation. Cilostazol treatment may be beneficial for the prevention of neurologic deficits after surgeries for descending aorta and thoracoabdominal aorta pathologies.

REFERENCES


