Revolutionizing Carotid Artery Disease Treatment: Advancement in Self-Expandable Stent with Biodegradable Mesh Covering

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Abstract- Carotid atherosclerotic disease, characterized by the accumulation of plaque in the carotid arteries, poses a significant risk of stroke due to reduced blood flow to the brain. This research article presents a groundbreaking study focusing on the development of a novel self-expandable stent designed specifically for the carotid artery. The stent, composed of a nitinol alloy, incorporates a biodegradable mesh made of Poly(lactic-co-glycolic acid) (PLGA). Its tapered design ensures optimal alignment with the carotid artery’s natural anatomical attributes. The primary objective of this stent system is to enhance performance by minimizing restenosis and stent thrombosis occurrences. The biodegradable mesh covering creates a favorable environment within the blood vessel, effectively reducing the risk of clot formation. This is of utmost importance as clots can lead to severe complications such as vessel blockages, heart attacks, or strokes. The research significantly contributes to ongoing efforts in improving treatment options for carotid atherosclerotic disease and mitigating associated risks. Through meticulous in-vitro studies, the real-time degradability of the biodegradable polymeric mesh has been successfully assessed, laying the foundation for potential clinical applications. The development of this self-expandable stent offers a promising solution for patients suffering from carotid atherosclerotic disease. Its unique design, coupled with the biodegradable mesh, aims to enhance long-term efficacy, minimize complications, and improve overall patient outcomes. Our future studies would focus on rigorous in-vivo evaluations and clinical trials to further validate the potential of this stent in revolutionizing the treatment landscape for carotid atherosclerotic disease.

Keywords: Carotid atherosclerotic disease, Plaque accumulation, Carotid artery, Nitinol stent, Biodegradable PLGA mesh, Tapered design, Restenosis, Stent thrombosis and In-vitro studies.

1. Introduction:
Carotid artery disease occurs when the carotid arteries, responsible for delivering blood to the brain and head, become blocked by plaque, which consists of fatty deposits. This obstruction significantly increases the risk of stroke, a critical medical condition that arises from a substantial reduction or complete loss of blood supply to the brain. Approximately 2-4% of individuals aged 65 and above have carotid artery narrowing exceeding 50%. Without sufficient blood or oxygen, brain cells begin to die within a few minutes. The narrowing of carotid arteries can impede blood flow, potentially leading to a stroke. Moreover, the detachment of a plaque fragment can also cause a stroke by blocking the blood flow to the brain. Addressing the consequences of carotid artery disease is of utmost importance for various reasons. It aids in stroke prevention, preservation of brain function, improvement of quality of life, and long-term management of cardiovascular health. By managing the disease's effects, individuals can reduce potential risks, enhance overall well-being, and enjoy a better quality of life.

A laser-cut carotid stent made up of a nitinol alloy is a medical device used in the present research study to treat carotid artery disease. Laser cutting technology has revolutionized the development of carotid stents, enabling precise shaping and customization of nitinol material resulting in stents with high structural integrity and dimensional accuracy. Laser cutting involves the use of a high-powered laser beam to precisely cut and shape materials, allowing for the creation of intricate designs and customized stent structures. The nitinol laser-cut carotid stent is fabricated from a nitinol alloy known for its strength, durability, and excellent biocompatibility. Nitinol alloy stents are safe and feasible to be used in carotid stenting. However, complications such as early stent thrombosis, late stent thrombosis and restenosis remain concerns.

To address this complication, the application of a mesh covering on the stent offers multiple benefits in mitigating early stent thrombosis, late stent thrombosis, and restenosis. The mesh covering, is often made of materials such as PLGA (Poly(lactic-co-glycolic acid), PTA (Polyethylene terephthalate), PET (Polyester), PTFE
(Polytetrafluroethylene). It acts as a physical barrier that helps to prevent platelet aggregation and clot formation on the stent surface. By inhibiting direct contact between blood components and the stent struts, the mesh reduces the risk of early thrombosis and improves the safety of the procedure.

Late stent thrombosis, a complication that can manifest months or even years after stent implantation, is often associated with delayed healing and incomplete endothelialization of the stent. The mesh covering promotes a more favorable healing response by facilitating the recruitment and proliferation of endothelial cells. These cells play a crucial role in the formation of a healthy endothelial layer on the stent. Consequently, this mitigates the risk of late thrombotic events.

Restenosis, characterized by the re-narrowing of blood vessels due to excessive neointimal tissue growth, is a prevalent issue following stent placement. The inclusion of a mesh covering can serve as a scaffold that limits neointimal hyperplasia by physically restraining excessive cell migration and proliferation. This mechanical restraint mechanism effectively curbs the formation of excessive tissue, thereby addressing the concern of restenosis.

Present research work proposes the incorporation of a nitinol stent having tapered configuration with a biodegradable polymeric mesh covering that closely conforms to the natural artery anatomy is likely to promote optimal functionality and reduce complications. The hypothesis suggests that the tapered design optimized functionality and could reduce complications by maintaining favorable blood flow dynamics, reducing the probability of blood clot formation and stent migration. Additionally, the meticulous engineering of the stent to achieve a secure fit is expected to enhance treatment outcomes in the bifurcated carotid artery.

2. Materials and Method

2.1 Design and Fabrication of Tapered Stent:

Carotid stent systems constitute a specialized subgroup of medical devices that fall under the category of self-expanding stent systems made from straight either tapered nitinol material. Carotid stent systems are designed to be tapered, with a larger diameter at the proximal end (where the stent is inserted) and a smaller diameter at the distal end (where the stent terminates). This design is intended to match the natural taper of the carotid artery, which can help to prevent stent migration. Figure.01 Provides a Depiction of the Construction and Configuration of the Stent Apparatus.

To create the structure of the stent, a super elastic nitinol tube (Memry Corporation, USA) is employed, which possesses an inner diameter free from oxides and an outer diameter surface that has been centerless ground. The stent is shaped using a laser cutting machine (Swiss Tech, Switzerland), afterwards we perform pre-cleaning to remove any unwanted barbs or excess materials that may be stuck in the stent. Subsequently, the stent undergoes grinding to eliminate any minute undesired particles present on its outer and inner surfaces.

Next, the stent is placed onto a mandrel with the desired diameter. The mandrel employed was purposefully designed with a tapering contour to effectively accommodate the tapered configuration of the stent. Additionally, a shape-setting process is conducted using a shape setting machine (Nagman Instruments, India) to secure and maintain the stent’s tapered shape. This process involves subjecting the stent to a temperature of 510°C for a duration of 5 minutes, which helps restore the stent to its original shape.

To achieve a smoother outer surface, the stent is subjected to sandblasting process. This process involves the use of abrasive particles propelled at high speed against the stent's outer surface, resulting in the removal of any roughness or irregularities.

The final step in development of stent is Electro-Polishing. This process aims to create a mirror-like surface on the stent's dull metals by selectively eliminating specific particles from its outer surface. When a direct electric current (DC) is applied, ions on the metal's surface undergo controlled oxidation and dissolution, resulting in the creation of a highly reflective surface. Figure.02 depicts a ‘Self Expanding Embolic Protection Stent Having Tapered Configuration’.
2.2 Opting for PLGA Polymer as a Superior Choice for Mesh Development:
The biodegradable polymeric knitted mesh covered on a self-expanding embolic protection stent constructed using a material that degrades once the risk of early stent thrombosis has been eliminated. Over the past two decades, significant progress has been made in the development of biodegradable polymeric materials for biomedical purposes. Biodegradable polymeric biomaterials are the preferred choice for creating therapeutic devices such as vessel scaffolds and sustained release drug delivery vehicles. These applications require materials with specific physical, chemical, biological, biomechanical, and degradation properties to ensure effective therapy. The material should be capable of undergoing degradation through hydrolysis or enzymatic processes, making it biocompatible with the human body.

One such copolymer used extensively in the current research study is an approved therapeutic device namely ‘poly(lactic-co-glycolic acid)’ or PLGA (Biogeneral Inc., USA). Its biodegradability and biocompatibility make it a suitable choice for various medical applications.

PLGA is synthesized by ring-opening copolymerization of two monomers: the cyclic dimers (1,4-dioxane-2,5-diones) of glycolic acid and lactic acid. Polymers can be synthesized as random or block copolymers, offering different polymer properties. Common catalysts used in the polymer's preparation include tin(II) 2-ethylhexanoate, tin(II) alkoxides, or aluminum isopropoxide. During polymerization, successive monomeric units of glycolic or lactic acid are linked together via ester linkages, resulting in a linear, aliphatic polyester.

2.3 The Power of Knitting Technology: Harnessing the Potential of covering 28-Micron PLGA Mesh:
2.3.1 Knitting Process:
To prepare and knit a polymeric mesh using a 28 microns thick PLGA (polylactic-co-glycolic acid) filament through knitting machine (Lamb Knitting Machine Corporation, USA) shown in the figure.03, several steps were followed. First, the machine was set up and checked for proper functioning. The required components, including needles and yarn guides, were put in place. A suitable polymeric yarn was chosen, considering strength and durability. The yarn's compatibility with the machine was ensured. Stitches were cast on and a stitch pattern was determined and programmed into the machine. The knitting process began, with the machine operating in rounds to form a continuous mesh tube. Monitoring and adjustments were made to maintain proper stitch formation, tension, and speed. Inspections were conducted to detect any defects, and necessary repairs were made. Knitting continued until the desired size was achieved. Finally, the finished mesh was carefully removed resulting in a versatile and functional polymeric knitted mesh fabric shown in the figure.04
The selection of a 28-micron PLGA mesh is based on several factors. Firstly, it undergoes a gradual degradation process over approximately 7 months, making it suitable for applications where the mesh needs to be absorbed or replaced by new tissue in the body. Secondly, the PLGA mesh surpasses that of other materials like PLLA, PCL and PTFE, even at the same thickness. This inherent strength is essential for providing structural support or reinforcement in various medical or industrial applications. Furthermore, the PLGA mesh exhibits biocompatible, ensuring it is well-tolerated by the body without causing any adverse reactions or harm to surrounding tissues. This biocompatibility makes it ideal for use in medical implants or devices that come into contact with living organisms. Lastly, the PLGA mesh can be safely eliminated from the body through a process known as hydrolysis. Hydrolysis is a chemical process in which a substance breaks down with the help of water. In this case, in addition, the filament used in creating the mesh boasts exceptionally smooth surface. Despite its smoothness, it retains enough strength to effectively serve its intended purpose. This smoothness is advantageous as it reduces friction and irritation when the mesh interacts with surrounding tissues or structures. Overall, the passage emphasizes the specific characteristics and advantages of utilizing a 28-micron PLGA mesh produced using knitting technology to cover it on a nitinol alloy stent.

2.4 Covering a Biodegradable Polymeric 28 Micron PLGA Mesh onto a Nitinol Stent:

2.4.1 Placing the knitted mesh: The prepared mesh was placed meticulously over the bare metal stent using a microscope to ensure accuracy due to small and delicate nature of the material involved.

2.4.2 Stretching and adjustment: The mesh was then stretched and adjusted to completely cover the stent.

2.4.3 Stitching the mesh: To fix the mesh in place, mesh was stitched with the help of forceps and micro-scissors over the stent using a same monofilament (poly (lactic-co-glycolic acid) (PLGA)).

2.4.4 Eliminating extra material: After stitching, there may be excess mesh material on both edges. This extra material was carefully removed using the micro-scissors. This step ensured a snug fit of the mesh around the stent without any loose end.

2.4.5 Tying loose ends: Finally, the loose ends of the mesh were tied onto the struts of the stent. This tying process further secures the any movement or detachment of mesh from the stent. The overall process involved meticulous handling of the polymeric mesh and stent, along with precise stitching and trimming using specialized tools under a microscope. This ensures proper attachment of the mesh to the stent, creating a complete covering and fixation as shown in the figure.05 that is crucial for its intended function. The complete implant assembly namely ‘Self Expanding Embolic Protection Stent with a biodegradable polymeric knitted mesh covering’ is depicted in the figure.06.
Figure.06 Illustrates a Perspective View of an Exemplary Embodiment of the research, showcasing a Knitted Porous Structure Enhanced Stent Apparatus in an Open Mode

2.5 Delivery System
2.5.1 An Access for Delivery System
The carotid area, being a highly sensitive region near the brain, necessitates a delivery system that is responsive to control and as compact as possible. With careful consideration of all the requirements, a system has been designed specifically for delivering the ‘Biodegradable Mesh Covered Self Expanding Embolic Protection Stent’ with precision to the desired location.
Based on the information given, the surgeon can decide whether to insert the aforementioned implant through either the femoral artery or the subclavian artery in the patient's arms. This decision depends on the surgeon's expertise and the accessibility of these arteries. In present study, a specific type of delivery system called an Rx (Rapid Exchange) Delivery System has been designed and utilized. This delivery system is designed to work with a 0.014” guide-wire, which would serve as a navigational tool during the procedure. The outer profile of the delivery system is 6 French (Fr), which indicates the diameter of the catheter shaft. This size is important for ensuring compatibility with the patient's blood vessels.
Furthermore, the length of the delivery system has been kept as 1420 mm. This measurement refers to the overall length of the system and helps the surgeon determine how far the device can reach inside the patient's body during the procedure.

2.6 Delivery Process
2.6.1 Arterial Access: In order to access the carotid artery, a puncture can make from the groin area to reach the femoral artery, which serves as the entry point for the delivery system.
2.6.2 Insertion of Sheath: An introducer sheath, a thin hollow tube, was used to facilitate the passage of the catheter. The diameter of the catheter used in this system was usually 6 French.
2.6.3 Adjusting Puncture Size: If the hole size is not large enough for the catheter, a dilator is used. The dilator gradually increases the size of the puncture hole up to the required diameter, allowing the smooth passage of the catheter.
2.6.4 Placement of Guide wire: Once the introducer sheath is in place, a 0.014” guide-wire is inserted through the sheath. The guide-wire acts as a pathway, helping navigate the delivery system to the target location within the carotid artery.
2.6.5 Advancing the Delivery System: The delivery system, consisting of the stent and the catheter, was then advanced over the 0.014” guide-wire. The professional carefully guides the system through the artery until it is perfectly positioned at the target site.
2.6.6 Stent Deployment: To deploy the stent, the delivery system incorporated a roller mechanism. The professional held the system steady and used their thumb to roll the roller backward. This action triggered the deployment of the stent, releasing it from the catheter and allowing it to expand against the artery walls.
Ensuring proper placement: Throughout the process, the professional ensures that the delivery system remains stable and precisely positioned at the target site. This was crucial to ensure accurate deployment of the stent and optimal restoration of blood flow through the carotid artery.
By carefully following these steps using the aforementioned delivery system, professionals were able to effectively treat blockages in the carotid arteries and improve blood flow to the brain, reducing the risk of stroke or other complications.

3. Results and Discussion
The inclusion of a mesh covering on a stent is of utmost importance to prevent early stent thrombosis, restenosis, and other complications. Early stent thrombosis refers to the bursting of plaque deposits shortly after stent implantation. When plaque deposits remain stable within the artery wall, they can obstruct blood flow, potentially leading to severe outcomes such as stroke and even mortality. However, the introduction of a mesh-covered stent effectively clears the blockage, allowing the artery to expand, while accommodating the plaque along the side wall of the arteries,
eventually leading to thrombus formation within the artery wall. This condition, known as early stent thrombosis and typically occurs within the first three months after stent placement. To minimize the occurrence of early stent thrombosis, a mesh is incorporated onto the stent to mitigate the risk.

Our hypothesis suggests that early stent thrombosis is more likely to occur within the first three months because, during this period, rendering them more susceptible to potential disruptions. However, once the plaque becomes fully integrated and forms part of the arterial epithelium, the need for the mesh diminishes, allowing it to gradually degrade within the patient's body. The mesh is typically composed of biodegradable materials, enabling natural breakdown through the body's physiological processes.

To assess the degradation of the mesh and predict its in-vivo degradability, we conducted comprehensive in vitro studies, closely mimicking the conditions within the human body. These meticulous assessments provided valuable insights into the mesh's degradation over time once implanted in a patient, contributing to advancements in stent technology and patient care. The results of this study highlight the importance of mesh-covered stents for enhancing treatment outcomes and reducing complications related to early stent thrombosis and restenosis.

3.1 Investigating of the Structural Integrity and Durability of Covered Polymeric Mesh on a Self Expanding Embolic Protection Stent: In-vitro Test Performance Analysis:

The soaking solution (PBS) was prepared using analytical grade KH2PO4 and Na2HPO4 salts, which were dried to a constant mass. To prepare Solution A, 4.539 g of Potassium dihydrogen phosphate (KH2PO4) was dissolved in 500 ml of double distilled water, resulting in a final concentration of 1/15 mol/litre. Solution B was prepared by dissolving 17.801 g of dibasic Sodium hydrogen phosphate anhydrous (Na2HPO4) in 1500 ml of double distilled water, also resulting in a concentration of 1/15 mol/litre. The buffer solution was made by mixing 273 ml of Solution A (18.2% v/v) and 1227 ml of Solution B (81.8% v/v) to a total volume of 1500 ml. The pH of the buffer solution was measured to be 7.38. Finally, the buffer solution was filtered through a 0.22 μm filter to prevent microbial contamination.

Two distinct glass vials were prepared for the test samples. Each vial contained 10 ml of the soaking solution. The test samples were mounted on Teflon stylets and placed inside the vials to ensure complete submersion in the soaking solution. To prevent evaporation of the solution, the vials were tightly sealed with silicon stoppers, as depicted in Figure 07. The vials, with the test samples inside, were then placed in a hot air oven set at a constant temperature of 37°C ± 1°C. At regular intervals, the samples were retrieved from the soaking solution for further analysis.

On a daily basis, we extracted samples from the soaking solution and visually inspected them using an optical microscope set at 40X magnification. The objective was to assess the integrity of the sample. To enhance visibility, we carefully dried the surface of the mesh with a paper towel. We meticulously recorded the structure, geometry, aperture, dimensions, as well as any breaks or cracks in the monofilaments of the knitted mesh. The real-time degradation study concluded once the knitted mesh had completely disintegrated. The visual observations from the degradation study were documented at regular intervals and summarized in Table.01. Corresponding images are presented in Figures 08, 09, 10, and 11.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Real Time IVD Days</th>
<th>Analysis of degradability of knitted mesh</th>
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<tr>
<td></td>
<td></td>
<td>Sample No.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample No.2</td>
</tr>
<tr>
<td>Sample No.</td>
<td>Observation</td>
<td></td>
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<tr>
<td>------------</td>
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<td></td>
</tr>
<tr>
<td>Sample No.1</td>
<td>Knitted mesh covered on self expanding stent</td>
<td></td>
</tr>
<tr>
<td>Sample No.2</td>
<td></td>
<td></td>
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**Table.01 Visual observation during Real-Time degradation study**

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Observation</th>
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<tbody>
<tr>
<td>1</td>
<td>Initial Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>2</td>
<td>03 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>3</td>
<td>12 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>4</td>
<td>17 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>5</td>
<td>21 days Knitted mesh with no breakage or damage</td>
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<tr>
<td>6</td>
<td>35 days Knitted mesh with no breakage or damage</td>
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<tr>
<td>7</td>
<td>42 days Knitted mesh with no breakage or damage</td>
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<tr>
<td>8</td>
<td>49 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>9</td>
<td>56 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>10</td>
<td>63 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>11</td>
<td>70 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>12</td>
<td>105 days Knitted mesh with no breakage or damage</td>
</tr>
<tr>
<td>13</td>
<td>153 days Knitted mesh completely solubilized</td>
</tr>
<tr>
<td>14</td>
<td>167 days Bulk erosion of knitted mesh</td>
</tr>
<tr>
<td>15</td>
<td>201 days Bulk erosion of knitted mesh</td>
</tr>
</tbody>
</table>

**Sample No.1**

**Observation**: Knitted mesh covered on self expanding stent
Figure.08 The microscopic images of the test samples from an initial day to 105 days

**Sample No.1**

**Observation**: Instances of breaks in the structure of the knitted mesh structure at 153 days

**Sample No.2**

**Observation**: Instances of breaks in the structure of the knitted mesh structure at 153 days
<table>
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<tr>
<th>Sample No.1</th>
<th><img src="image1.png" alt="Image" /></th>
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<tbody>
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<td><strong>Observation</strong>: Bulk erosion of the knitted mesh was observed till 167 days.</td>
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<td><strong>Observation</strong>: Bulk erosion of the knitted mesh was observed till 167 days.</td>
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Figure 10: The microscopic images of the test samples at 167 days

<table>
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<th>Sample No.1</th>
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<tbody>
<tr>
<td><strong>Observation</strong>: Knitted mesh underwent complete solubilization after 06 months, i.e. at 201 days</td>
<td></td>
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| Sample No.2 | ![Image](image4.png) |
4. Conclusion
In conclusion, the research study on the development of a ‘self expanding embolic protection stent with a biodegradable polymeric knitted mesh’ has provided valuable insights into its in vitro performance and durability for treating carotid atherosclerotic arteries. The study reveals the compatibility of the mesh with the soaking solution, without impacting pH levels. The knitted mesh exhibited remarkable structural integrity for up to 105 days, with no observed breakages or damages. However, vulnerability became evident at 153 days, as certain mesh apertures showed signs of breakage. The situation worsened by 167 days when the mesh collapsed due to aperture fractures, underscoring the necessity for careful consideration of the degradation timeline and associated risks. The most significant finding of this study was the complete solubilization of the knitted mesh after six months, precisely at 201 days. This highlights the importance of comprehending the mesh's time-dependent degradation characteristics to ensure its long-term safety and effectiveness for patients. The forthcoming publication of the pre-clinical study data will provide a comprehensive and valuable resource for researchers and medical professionals, further advancing the understanding and development of an embolic protection stent system for the treatment of carotid atherosclerotic arteries.

REFERENCES: