(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 7, Issue 5 , Page No: 254-262
September-October 2024

IJMSCR

Efficacy of a Developed Self-Expandable Braided Metallic Biliary Stent System for Alleviating Cholestasis in Bile Cancer Patients: An In-Vitro Test Assessment

Dr. Minocha Pramodkumar, Kothwala Dr. Deveshkumar Mahendralal, Solanki Himanshu Rajesh, Patel Viral Naresh & Gautam Khushbu Dineshkumar
Meril Medical Innovations Private Limited, Bilakhia House, Survey no.879, Muktanand marg, Chala, Vapi, Dist-Valsad, Gujarat, 396191, India. E-mail:mansi.desai@merillife.com

***Corresponding Author:**
Dr. Minocha Pramodkumar
Meril Life Sciences Pvt. Ltd., Bilakhia House, Survey No.135/139, Muktanand Marg, Chala, Vapi - 396191, Gujarat, India

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

A biliary stent, also referred to as a bile duct stent, is a slender, hollow tube inserted into the bile duct to maintain its openness following blockage or partial obstruction. The resulting obstruction leads to a serious health issue called Cholestasis, marked by significant challenges in digesting food. Bile ducts facilitate the flow of fluids like bile into the intestine, crucial for digestion. Cholangiocarcinoma, or bile duct cancer, arises from abnormal cellular changes in the bile duct lining, resulting in uncontrolled tumor growth. The obstruction of bile ducts induces the risk of bacterial infections such as cholangitis, leading to the symptoms like digestive disturbances, fever, weight loss, abdominal pain, and jaundice. To address the cholangitis in bile cancer patients, this research study presents a "Self-Expandable Braided Metallic Biliary Stent System." The developed stent system offers palliative therapy by effectively widening narrowed bile pathways, alleviating the effects of cancer-induced constriction. Positive outcomes from controlled laboratory tests, specifically in-vitro studies, support this research. These studies assess the efficacy and performance of the "Self-Expandable Braided Metallic Biliary Stent System" under simulated conditions, providing promising evidence of its effectiveness and potential benefits for patients with bile cancer and cholangitis.

Keywords: Cholangiocarcinoma, Cholangitis, Palliative Therapy, and Self-Expandable Braided Metallic Biliary Stent System

Introduction

Bile ducts are elongated tubular structures that facilitate the transport of bile from the liver and gallbladder to the small intestine, integral to the digestive process. These bile ducts branch extensively to form a network known as the biliary tree *(Song, Ge, Hugh Q. Zhao, Qing Liu, and Zhongyong Fan, 2022)***.** The common bile duct is a slender tubular conduit, averaging 7.5 to 11 centimeters in length and 6 to 8 millimeters in diameter, which facilitates the transportation of bile from the gallbladder to the duodenum. Complex clinical pathologies may lead to narrowing or stenosis of the bile duct lumen, resulting in obstruction of normal bile flow. Bile duct stenosis can be either benign or malignant. In the absence of appropriate clinical intervention, biliary stricture can cause compromised liver function, secondary biliary cirrhosis, and, ultimately, may result in mortality *(Yan Zhang, Hexuan Jiang, 2023).* Forming an integral component of the gastrointestinal (GI) tract, commonly referred to as the digestive system, Bile ducts are tiny canals that connect some of the organs in your digestive system. Their purpose is to carry bile between these organs.

However, the emergence of bile duct cancer disrupts this harmonious functionality, giving rise to a distressing condition marked by the uncontrolled proliferation of malignant cells within the bile tissues. As these aberrant cells multiply and coalesce, they form malignant tumors that progressively constrict the bile duct. Biliary stricture can be caused by various diseases and the majority of biliary strictures are malignant *(J. S., Jeong, S., Lee, D. H., Jeong, T., Ki, B., Paik, W. H., Ryu, J. K., & Kim, Y, 2023)*. The ensuing blockage engenders a debilitating medical complication known as Cholestasis, characterized by the profound difficulty in food digestion.

Malignant biliary obstruction is often caused by pancreatic carcinoma, cholangiocarcinoma, and metastatic disease. The majority of these patients will require non-surgical treatment because of the advanced nature of the disease or significant co-morbidity associated with surgery *(J., Han, Z., & Yang, J, 2014)*. In response to this, a formidable challenge aimed at addressing the Cholestasis in patients afflicted by bile cancer is introduced.

The present research study focuses on developing a medical solution termed the "Self-Expandable Braided Metallic Biliary Stent System" which is composed of a nitinol alloy. A stent is a tubular device made of plastic or metal, which is used to maintain the patency of a lumen *(Sturgess R, 2008)*. This approach is poised to revolutionize palliative care for individuals suffering with the impediments wrought by bile cancer-related obstructions. In contrast to stainless steel stents (traditional stents) with their rigid composition and limited flexibility, the innovation in stent technology has spurred the exploration of alternative options. Nickel titanium, commonly referred to as nitinol, emerges as a prominent alternative. Nitinol, a nickel-titanium alloy, showcases remarkable characteristics including the shape memory effect and super-elasticity *(Bonsignore C, 2003)*. This alloy can undergo significant deformation and swiftly revert to its original form upon external load removal, surpassing the capabilities of traditional metals. The transformation between its deformed and ordered phases at specific temperatures further amplifies its applicability in medical stents.

The main objective of the proposed stent system is to open up a blocked or narrowed bile duct. This is essential for preventing complications associated with bile duct obstruction. This technique entails the placement of a specially designed stent within the constricted bile duct. A key distinctive feature of this stent is the incorporation of flared ends, strategically integrated into the stent's design. These flared ends prevent the undesirable migration of the stent post-implantation, ensuring its stable positioning and enhancing its enduring efficacy in ameliorating symptoms.

Beyond its design, this minimally invasive technique represents non-surgical therapeutic options. By its mechanical strength capability and secure anchoring mechanism, the stent system presents a minimally invasive yet profoundly transformative solution for the debilitating condition of bile duct cancer-induced Cholestasis. This advancement heralds a new era in palliative care, underscoring its potential to vastly enhance the quality of life for patients who are grappling with the complications of bile duct cancer. In addition to its design and minimally invasive nature, the effectiveness of the "Self-Expandable Braided Metallic Biliary Stent System" has been further evaluated through rigorous laboratory testing.

In-vitro studies have yielded positive outcomes, demonstrating the stent's ability to effectively open blocked or narrowed bile ducts. These findings provide compelling evidence of the stent's potential to alleviate symptoms associated with bile duct obstruction, offering renewed hope to patients suffering from bile duct cancer and cholangitis. With its promising performance and durable anchoring mechanism, this stent system represents a significant advancement in palliative care for individuals grappling with the debilitating effects of bile duct cancer-induced cholestasis.

Materials and Method

The characteristics of stent flexibility, resistance to migration, and precision are intricately linked to the specific construction approach and design structure of the device. In this context, stents developed through braiding exhibit a combination of qualities. These stents possess a significant radial expansive force, contributing to their capacity for dilation, while concurrently retaining a remarkable degree of flexibility. The architecture of braided stents allows the constituent wires to move freely at their points of intersection. This unique attribute facilitates the stent's ability to adapt and conform to the dynamic

Volume 7, Issue 5; September-October 2024; Page No 254-262

contractions of the bile duct muscles, ensuring optimal accommodation within the physiological context.

The manufacturing process of stents encompasses several essential stages. These include braiding, a technique that interlaces wires to form the stent's base structure, resulting in its characteristic radial force and flexibility. Subsequent to this, shape setting ensures that the stent acquires its intended form and dimensions. Back braiding and another step, laser welding refines the stent's structural integrity by optimizing the arrangement of wires. Additionally, chemical passivation serves to enhance the stent's biocompatibility and corrosion resistance, ensuring its safety within the body. Collectively, these manufacturing stages culminate in the production of stents that embody the crucial attributes of performance, adaptability, and safety within the physiological environment.

Development of 'Self-Expandable Braided Metallic Biliary Stent System

Braiding:

The execution of the braiding process took place using a specialized 32-carrier wire braiding machine. For support and structural integrity, an SS316L Mandrel was employed. Within this procedure, a total of 8 nitinol wire intricately interwove with each other. The interlacing process initiated from a single side of the mandrel, where the nitinol wires were systematically intertwined, and giving rise to a coherent and well-structured pattern. This precise sequential methodology led to the formation of a braided configuration, possessing the desired attributes of strength, flexibility, and radial expansion potential. These attributes are of utmost importance for the subsequent application of the stent.

Primary shape setting:

The shape setting process termed as primary shape setting, involved strategically manipulating braided nitinol stent. This manipulation was achieved by securely immobilizing the nitinol stent onto a mandrel or fixture affixed in shape setting machine that mirrored the intended final shape.

A heat treatment (ranging from 500-550 degree Celsius) was administered to initiate the shape-setting transformation. This heat treatment methodology, shared by both the shape memory and super-elastic variations of nitinol, ensured the precise establishment of desired shapes. This controlled thermal process assumed a pivotal role in enabling the nitinol stent to consistently exhibit the specified shape memory or super-elastic characteristics, rendering it well-suited for its designated application.

Manual back braiding:

The manual back braiding technique secured the loose end of a wire by weaving it together with each other from another side through the support of mandrel. This created a closed and secure end that prevented the wire from unraveling or coming loose in the future. The process involved a series of steps. It started by the loose end of long extended wire remaining after braiding process. The wires were placed side by side on a work surface for consistency, and fingers or pliers were used for control, especially with thin wires. The intertwining began by crossing the wires at an angle to make an "X" shape.

Holding the cross, the wires were twisted together by hand, ensuring a consistent weave. This motion created a strong braiding pattern that continued as the wires were twisted and crossed along the loose end's length. Keeping the right tension was important, helped by fingers or pliers for guidance. Progressing to the end of the loose wire, the intertwined wires formed a closed and tight finish. To complete the process, any extra braiding material was trimmed for a neat appearance. It was essential to have a flawless, secure braided section without any loose parts. After braiding, a thorough inspection confirmed its strength, and a gentle pull test verified the effectiveness. This method guaranteed wire terminations that resisted unraveling, proving crucial for secure wire ends in various applications.

Secondary shape setting:

The stent that underwent manual back braiding then proceeded to a secondary shape-setting process, similar to the primary shape setting procedure. In the context of this research, the objective of secondary shape setting process was to replicate the shape of the back-braided wires achieved by manual back braiding.

Laser welding:

Following the back braiding and secondary shape setting process, laser welding process was carried out. The stent was cleaned to eliminate any potential debris

Volume 7, Issue 5; September-October 2024; Page No 254-262

or contaminants that could have compromised the weld quality. The stent was then positioned and aligned with precision to guarantee accurate welding results. The subsequent step involved the setup of the laser welding equipment.

This entailed configuring specific laser parameters based on factors like the stent's material composition and the desired quality of the weld. These parameters encompassed variables such as power level, pulse duration, beam diameter, and scanning speed.

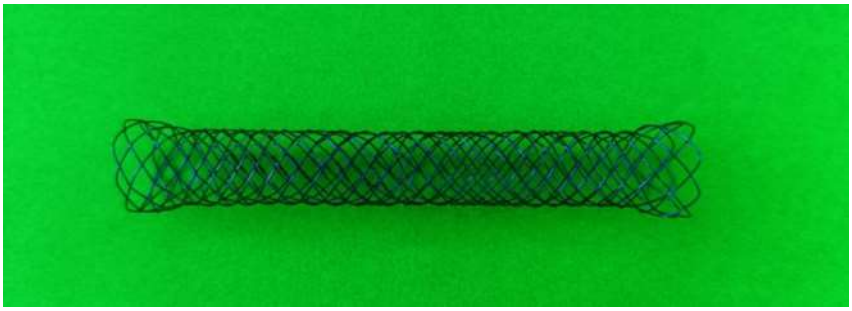
Moving to the core welding process, the laser beam was focused on the designated joint area where the segments of the back-braided stent needed to be seamlessly united. The concentrated energy delivered by the laser beam induced the targeted material to melt at the joint, generating a confined molten pool. As the laser beam traversed the joint, the molten material solidified progressively, culminating in the formation of a robust weld that effectively fused the stent segments together.

Chemical passivation:

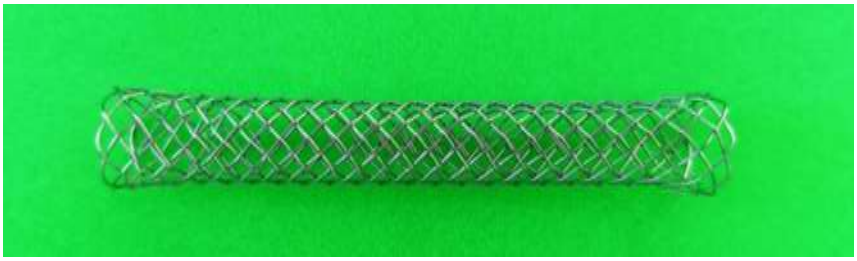
After the laser welding process, a chemical passivation procedure was undertaken, which involved thorough chemical cleaning and precisely controlled oxidizing treatment. The specialized chemical passivation equipment of the "2-MLH" model was utilized, using nitric acid (HNO3) to treat the stent. Nitric acid, recognized as a potent oxidizing agent, interacted with the surface of the stent, resulting in significant enhancements. Firstly, it eliminated impurities like free iron and nickel that could potentially cause corrosion and biocompatibility issues after implantation. Secondly, the treatment generated a protective layer, mitigating reactions with external elements and improving corrosion resistance. Lastly, this procedure reinforced the stent's structural integrity, ensuring optimal performance and durability within the body. This comprehensive passivation process guaranteed the stent's effectiveness, promoted patient well-being, and minimized potential complications. Passivation layer formation was confirmed by changing of stent color from metallic violate blue to Silver as shown in the **Figure.01**

Figure 01 (A) & (B) Biliary stents before and after undergoing the chemical passivation process respectively.

A



B



The delivery system accompanied by its component parts

Volume 7, Issue 5; September-October 2024; Page No 254-262

The "Biliary stent system" utilizes an efficient push-pull mechanism for accurate placement. The delivery system shown in the **Figure.02** consists of an 8.5Fr or 9Fr delivery catheter, pusher tube, inner tube, PT/IR markers. These components work together to ensure the precise and controlled positioning of the braided stent.

During the procedure, the peek victrex 381G Pusher tube facilitates a controlled and smooth pushing force, ensuring accurate delivery of the braided stent to the intended location for effective treatment.

To aid visualization and accurate placement, the system incorporates platinum radio-opaque marker rings on the braided tube and inner tube at three points, indicating the proximal, distal, and retrieval points. These markers are strategically positioned to provide clear and reliable radiographic guidance, enabling healthcare professionals to closely monitor stent placement within the bile duct. These markers significantly enhance stent visibility during fluoroscopy procedures, ensuring precise alignment and placement.

Figure.02 The delivery system designed for introducing the 'self-expandable braided metallic biliary stent system' into the bile duct

The Stent Loading:

The procedure begins with inserting the stent into the braided tube as depicted in **Figure.03.** Following this, the pusher tube is attached to the handle. Once the stent is firmly situated within the inner tube on the stent locker, the tube is carefully advanced towards the proximal end of the catheter. This deliberate action ensures the accurate loading of the stent within the tube, preparing it for insertion.

Figure.03 Stent integration within braided tube's inner lumen for secure and precise positioning, initiated proximally, advanced with careful alignment for seamless integration

By pulling the handle on the proximal side, the stent is partially inserted into the catheter, as illustrated in **Figure 04.** The stent can then be carefully retracted as required. This process reveals the stent loading procedure, improving visibility and control during the intervention.

Figure.04 Partial stent insertions into the catheter by manually pulling the proximal side handle to advance the stent into the catheter lumen in a controlled manner

Volume 7, Issue 5; September-October 2024; Page No 254-262

Upon full loading, as shown in **Figure.05**, this step finalizes the loading process, ensuring the braided stent is entirely prepared for deployment. At this point, the stent is optimally positioned within the catheter and has reached the intended location within the bile duct.

Figure.05 Final loading and optimal positioning of a stent into the catheter for deployment

Deployment and access point:

The delivery process of the "self-expanding biliary stent system" guarantees accurate placement and deployment of the braided stent at the intended location. The stent is delivered through a dedicated system, as depicted in the **Figure.06,** during ERCP (Endoscopic retrograde cholangiopancreatography) Procedure the stent is introduced via mouth using of 8.5Fr and 9Fr delivery system.

Figure.06 The complete assembly of a delivery system for delivering 'self-expandable braided metallic biliary stent system' into the bile duct.

Initially, a guide wire is carefully inserted to the desired target site, serving as both a pathway and a reference point for the subsequent delivery of the braided stent system. The insertion of the guide wire is guided by fluoroscopy, a real-time X-ray imaging technique that provides precise visualization of the guide wire's movement and positioning within the bile duct.

Once the guide wire is accurately positioned, it is guided to the target location using fluoroscopic imaging, ensuring precise placement within the bile duct. Subsequently, the braided stent system is delivered over the precisely positioned guide wire. The design of the braided stent allows it to self-expand upon deployment.

Further advancement involves maneuvering a catheter containing the braided stent over the guide wire. The catheter is carefully manipulated until the braided stent reaches its intended target site within the bile duct.

In summary, this delivery process guarantees the precise placement of the self-expanding bile duct stent system through the use of a guide wire, fluoroscopic guidance, and the self-expanding stent itself. The ultimate outcome is the accurate deployment of the stent to the specified location within the bile duct, facilitated by the ERCP Procedure using an 8.5Fr or 9Fr delivery system.

Result and Discussion

The in-vitro implantation of the Biliary self-expanding stent system within a simulated curvature model, designed to emulate conditions encountered in the human bile duct (in-vivo), yielded promising and noteworthy outcomes. Utilizing the specified delivery system, which included the pre-loaded implant, the implantation procedure proved to be remarkably intuitive and user-friendly, allowing for precise deployment at a predetermined location, referred to as the targeted site.

The process commenced with the cautious introduction of the catheter into the simulated curvature model, as vividly illustrated in **Figure.07**. Subsequently, the catheter was skillfully navigated to

Volume 7, Issue 5; September-October 2024; Page No 254-262

the intended location within the simulated curvature model, as depicted in **Figure.08**. This precise navigation corresponded precisely to the expected deployment site of the implant. Achieved through the manipulation of a user-friendly handle, this controlled deployment mechanism ensured the stent was accurately placed within the model at the desired location.

Figure.07 A simulated curvature model depicting the simulation of the bile duct system into which a catheter is inserted

Figure.08 Precise catheter navigation into intended location in curvature model

Upon deployment, the stent, which had been crimped for delivery, exhibited a remarkable capacity to return to its original shape, as clearly shown in **Figure.09**. This inherent ability of the stent to regain its initial configuration played a pivotal role in ensuring that the Biliary self-expanding stent system assumed an appropriate position within the simulated curvature model at the targeted site.

Figure.09 Stent regaining original shape after deployment

Moreover, the delivery components of the system were designed to provide enhanced flexibility and lubricity, facilitating seamless movement through the intricate pathways of the curvature model. Consequently, the friction encountered during delivery was substantially reduced compared to conventional delivery systems, contributing to the overall efficiency and precision of the implantation procedure.

In summary, the results obtained from the in-vitro implantation of the Biliary self-expanding stent system using the aforementioned delivery system within the simulated curvature model unequivocally demonstrated its effectiveness and its potential to

Volume 7, Issue 5; September-October 2024; Page No 254-262

enhance interventions within the bile duct. These findings provide robust support for its viability as a promising option for achieving successful implantation when applied in-vivo within the human bile duct.

Conclusion

In conclusion, our research underscores the promising potential of the Biliary self-expanding stent system as a critical intervention for addressing malignant bile duct strictures. This approach possesses several notable strengths, including its rapid deployment, cost-effectiveness, and demonstrated safety within a simulated curvature model. These findings raise optimism regarding the stent system's viability as an effective palliative therapy, capable of widening constricted bile duct passages and alleviating the effects of cancer-related constriction. The implications of our study are significant, contributing to our understanding of palliative treatments and laying the foundation for future pre-clinical investigations. Ongoing efforts will be instrumental in establishing the Biliary self-expanding stent system as a dependable and widely-adopted solution for managing malignant bile duct strictures. The integration of this implant with its delivery system into clinical practice has the potential to transform treatment approaches and improve long-term patient outcomes. In conclusion, our present in-vitro research study can serve as a valuable reference for future pre-clinical and clinical investigations involving the implantation of a Biliary self-expanding stents. It provides a foundation for advancing the field of bile duct cancer treatment, offering hope for enhanced patient care and well-being.

References

1. Song, Ge, Hugh Q. Zhao, Qing Liu, and Zhongyong Fan, (2022). “A Review on Biodegradable Biliary Stents: Materials and Future Trends.”. *Bioactive Materials*. https://doi.org/10.1016/j.bioactmat.2022.01.017.
2. Qi Zhang, Haipo Cui, Yan Zhang, Hexuan Jiang, Qi Zhang, Haipo Cui, Yan Zhang, Hexuan Jiang. “Research Progress on Biliary Stents.” *Progress in Medical Devices*, June 30, 2023. https://doi.org/10.61189/031576vfjfax.
3. Cho, I. R., Lee, S. H., Choi, J. H., Park, N., Lee, M. W., Kim, J. S., Jeong, S., Lee, D. H., Jeong, T., Ki, B., Paik, W. H., Ryu, J. K., & Kim, Y. (2023). Development of novel biliary metal stent with coil-spring structure and its application in vivo swine biliary stricture model. *Frontiers in Oncology*, *13*, 1103217. https://doi.org/10.3389/fonc.2023.1103217
4. Cui, J., Yao, J., Zhao, J., Han, Z., & Yang, J. (2014). Biliary stenting with or without sphincterotomy for malignant biliary obstruction: A meta-analysis. *World Journal of Gastroenterology : WJG*, *20*(38), 14033-14039. https://doi.org/10.3748/wjg.v20.i38.14033
5. Cui PJ, Yao J, Zhao YJ, Han HZ, Yang J. Biliary stenting with or without sphincterotomy for malignant biliary obstruction: A meta-analysis. World J Gastroenterol 2014.
6. Stern N, Sturgess R. Endoscopic therapy in the management of malignant biliary obstruction. Eur J Surg Oncol. 2008; 34:313-317.
7. Nga T. Nguyen, Hasan A. Khan, Kian Abdul-Baki, Woongsoon Choi, Neel K. Shroff, Zahra Akhtar, Peeyush Bhargava. CT imaging features of bile duct stent complications.
8. Knyrim K, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. Endoscopy. 1993;25:207-212.
9. Giorgio PD, Luca LD. Comparison of treatment outcomes between biliary plastic stent placements with and without endoscopic sphincterotomy for inoperable malignant common bile duct obstruction. World J Gastroenterol. 2004;10:1212-1214.
10. Krishnamoorthi R, Jayaraj M, Kozarek R. Endoscopic stents for the biliary tree and pancreas. Curr Treat Options Gastroenterol. 2017;15:397-415.
11. Yang MJ, Kim JH, Yoo BM, Hwang JC, Yoo JH, Lee KS, et al. Partially covered versus uncovered self-expandable nitinol stents with anti-migration properties for the palliation of malignant distal biliary obstruction: a randomized controlled trial. Scand J Gastroenterol. 2015;50:1490-9.
12. Knyrim K, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal

Volume 7, Issue 5; September-October 2024; Page No 254-262

stents for malignant obstruction of the common bile duct. Endoscopy. 1993;25:207-12.

13. Iwashita T, Yasuda I, Mukai T, Iwata K, Doi S, Uemura S, et al. Endoscopic ultrasound-guided antegrade biliary stenting for unresectable malignant biliary obstruction in patients with surgically altered anatomy: single-center prospective pilot study. Dig Endosc. 2017;29:362-8.
14. Hair CD, Sejpal DV. Future developments in biliary stenting. Clin Exp Gastroenterol 2013;6:91–99.
15. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. Lancet 1994;344:1655–1660.
16. Huibregtse K, Cheng J, Coene PP, Fockens P, Tytgat GN. Endoscopic placement of expandable metal stents for biliary strictures: a preliminary report on experience with 33 patients. Endoscopy 1989; 21:280–282.
17. Traina M, Tarantino I, Barresi L, et al. Efficacy and safety of fully covered self-expandable metallic stents in biliary complications after liver transplantation: a preliminary study. Liver Transpl 2009; 15:1493–1498.
18. Piñol V, Castells A, Bordas JM, Real MI, Llach J, Montañà X, et al. Percutaneous self-expanding metal stents versus endoscopic polyethylene endoprostheses for treating malignant biliary obstruction: randomized clinical trial. Radiology. 2002;225:27-34.
19. Dumonceau JM, Heresbach D, Deviere J et al. Biliary stents: models and methods for endoscopic stenting. European Society of Gastrointestinal Endoscopy (ESGE) Technology Review. Endoscopy 2011; 43: 617–626.
20. Raymondos K, Panning B, Bachem I et al. Evaluation of endoscopic retrograde cholangiopancreatography under conscious sedation and general anesthesia. Endoscopy 2002; 34: 721–726.
21. Katsinelos P, Kountouras J, Paroutoglou G et al. Uncovered Hanaro versus Luminex metal stents for palliation of malignant biliary strictures. J Clin Gastroenterol 2008; 42: 539–

Volume 7, Issue 5; September-October 2024; Page No 254-262