Volume 1, Issue 1, (2025)
1st May, 2025
DOI.org/10.71079/ASIDE.GI.1.1

ASIDE HEALTHCARE GASTROENTEROLOGY

PUBLISHED BY
AMERICAN SOCIETY FOR INCLUSION, DIVERSITY, AND EQUITY IN HEALTHCARE (ASIDE)

ISSN (Print) 3066-4004
ISSN (Online) 3066-4012

ASIDE Gastroenterology

Publisher

American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE).

ISSN (Print): 3066-4004, ISSN (Online): 3066-4012 – See front matter
https://doi.org/10.71079/ASIDE.GI.1.1
Journal homepage: https://asidejournals.com/index.php/Gastroenterology

Table of Contents

ISSN (Print): 3066-4004, ISSN (Online): 3066-4012 – See front matter
https://doi.org/10.71079/ASIDE.GI.1.1
Journal homepage: https://asidejournals.com/index.php/Gastroenterology

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Case Report

Usage of Trapezoid RX Wire guided Retrieval Basket with the Alliance™ II Inflation Handle for Treatment of Bouveret Syndrome: A Rare Clinical Entity.

Mahmod Ghoname [1], Hazem Abosheaishaa [2], Arshia Sethi [2], Sharif Abbas [3], Sherif Hegab [4], Moataz Yousry Soliman [1]*

1- Hepatology, Gastroenterology and Infectious Diseases Department, Al-Azhar University, Faculty of Medicine for Boys, Cairo, Egypt.
2- Internal Medicine Department, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals Queens, NY, USA.
3- Internal Medicine Department, Koc University School of Medicine, Istanbul, Turkey.
4- Hepatology, Gastroenterology and Infectious Diseases Department, Ahmed Maher Teaching Hospital, GOTHI, Cairo, Egypt.

ARTICLE INFO

Article history:
Received 14 Dec. 2024
Received in revised form 24 Dec. 2024
Accepted 27 Dec. 2024

Keywords:
Gallstones
Gastric outlet obstruction
Bouveret syndrome
Gastrointestinal

ABSTRACT

Bouveret Syndrome is an infrequent manifestation of gallstone disease causing gastric outlet obstruction. This syndrome has diagnostic and therapeutic challenges due to its rarity and non-specific clinical presentation. Here, we present a case report involving a 78-year-old female patient who experienced gastric outlet blockage due to the presence of a sizable gallstone. A novel technique was applied wherein a trapezoid RX wire-guided retrieval basket (Boston Scientific) was utilized with Esophagogastroduodenoscopy to remove the stone without the need for surgical intervention. Post-procedure monitoring demonstrated a smooth recovery with immediate relief of symptoms. Imaging confirmed the absence of residual gallstones or obstruction.

* ***Corresponding author:*** *Hazem Abosheaishaa, Department of Medicine, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals Queens, NY, USA.. Email Address: mailto: hazemabosheaishaa@gmail.com*

Citation: Ghoname M, Abosheaishaa H, Sethi A, Abbas S, Hegab S, Soliman MY. Usage of Trapezoid RX Wire guided Retrieval Basket with the Alliance™ II Inflation Handle for Treatment of Bouveret Syndrome: A Rare Clinical Entity. ASIDE GI. 2025;1(1):1-4. doi:10.71079/ASIDE.GI.0102255

https://doi.org/10.71079/ASIDE.GI.0102255
Journal homepage: https://asidejournals.com/index.php/Gastroenterology

1. Introduction

Bouveret syndrome (BS) is an uncommon manifestation of gallstone disease characterized by gastric outflow obstruction where the gallstone gets lodged in the duodenum or pylorus [1]. BS has been linked to a high mortality rate of up to 27% and can cause serious complications, particularly in elderly patients or those with comorbidities. Due to the rarity and non-specific presentation of BS, diagnosing it can be difficult [2]. A correct and prompt diagnosis is essential for enhancing prognosis, lowering morbidity, and preventing death [3]. Here, we present a case of BS with a large gallstone causing gastric outlet obstruction for which a trapezoid RX wire-guided retrieval basket (Boston Scientific) is used during EGD without surgical intervention.

2. Case Report

A 78-year-old female patient presented with a two-month history of worsening abdominal pain, nausea, and vomiting. The patient reported a decreased appetite and unintentional weight loss but no history of hematemesis, melena, dysphagia, fever, or rigors. Her medical history included type 2 diabetes mellitus, hypertension, ischemic heart disease, atrial fibrillation, NSAID due to sciatica, and a history of chronic calculous cholecystitis with an unremarkable surgical history. She was afebrile, slightly hypertensive, and with an irregular heart rate. Physical examination revealed abdominal distension and tenderness in the epigastric region with no organomegaly.

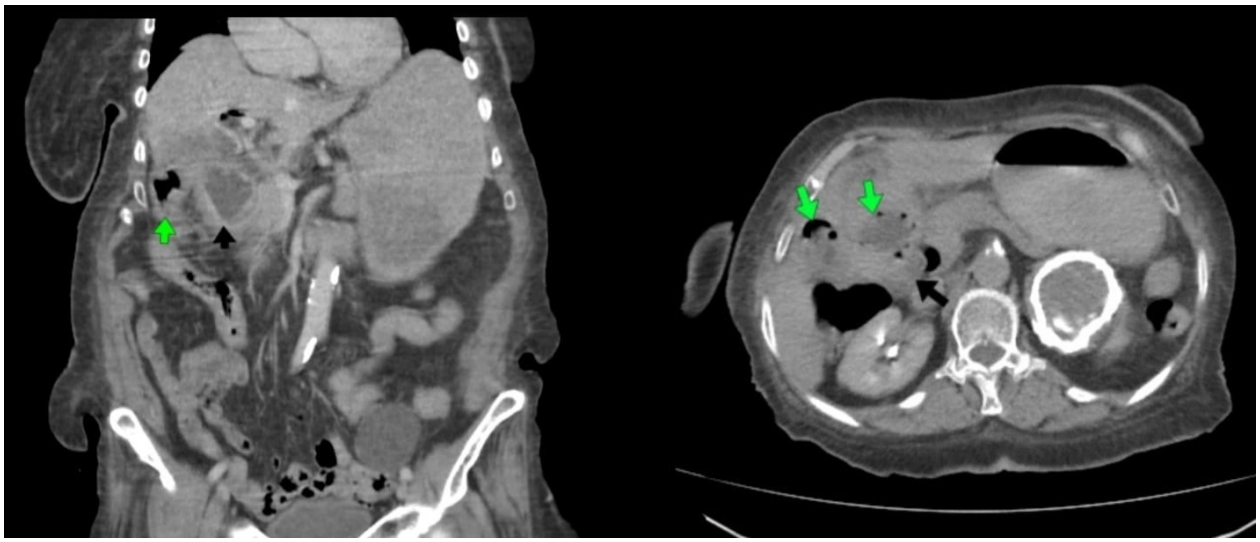

Figure 1: Multislice CT of the abdomen with oral and IV contrast showing partially distended irregular gall bladder containing multiple gas vacuoles (green arrows) which are seen compressing the second part of the duodenum (black arrows) with a fistulous track in between excreting proximal dilation of the stomach. Obvious pneumobilia is also seen.

On initial laboratory evaluation, she had a hemoglobin level of 9.3 g/dL and a white cell count of 15.3 × 109/L with elevated CRP 12 mg/dl. Serum creatinine was 1.4 mg/dL, and random blood sugar was 295 mg/dL with no acetone in urine. Her amylase and lipase were 52 U/L and 65 U/L, respectively. Bilirubin was normal with an alkaline phosphatase (ALP) level of 155 U/l (normal range, 40–120 U/l) and a γ-glutamyl transferase (GGT) level of 99 U/l (normal, <37 U/l). Diagnostic workup, including an abdominal X-ray and CT scan, confirmed the presence of a large gallstone causing gastric outlet obstruction with a fistulous tract between the gallbladder and the duodenum and a dilated proximal stomach (Figure 1).

After careful assessment and evaluation, an upper GI endoscopy was performed to relieve the gastric outlet obstruction. The gastroscope was inserted after endotracheal intubation, and the obstructing gallstone was visualized in the pyloric ring obstructing the lumen (Figure 2). We decided to use the trapezoid RX wire-guided retrieval basket (Boston Scientific), designed for crushing and removing stones in the biliary duct. We may use the Alliance™ II Inflation Handle for mechanical lithotripsy to crush large stones trapped within the basket with the scope in place. However, after several trials, stone extraction failed. So, we decided to try to mobilize the large stone to the stomach. The biliary extractor balloon catheter was inflated up to 18 mm distal to obstructing stone, and the stone was successfully retrieved into the stomach with difficulty. A trapezoid basket was introduced through the endoscope's working channel and used to crush, grasp, and extract the large gallstone, which measures 4 cm × 3.6 cm, and to facilitate the extraction of the stone through the cardia and esophagus without impaction or perforation. The remaining stones were retrieved without any complications (Figure 3). Finally, gastric outflow was restored after three hours of working in a single session.

The patient experienced immediate relief and post-procedure monitoring showed a steady recovery without any complications. The patient tolerated a regular diet, and subsequent imaging studies confirmed the absence of residual gallstones or signs of obstruction.

3. Discussion

Bouveret's syndrome (BS) is a rare subtype of gallstone ileus making up about 1%-3% of cases [4]. Repeated episodes of cholecystitis result in inflammation and adhesions between the gallbladder and the GI tract which most commonly involves the duodenum but can also involve the stomach. Pressure necrosis by fairly large calculus results in fistula formation which predisposes to a migrating calculus hence causing either obstruction or ileus [5].

BS is usually seen in elderly females, with a median age of 74 and a history of cholelithiasis or cholecystitis. Patients present with vague symptoms of gastric outlet or bowel obstruction that usually include nausea or vomiting and sometimes hematemesis or melena [5]. Non-

specific presenting symptoms not only make diagnosis challenging but also increase morbidity and mortality [4].

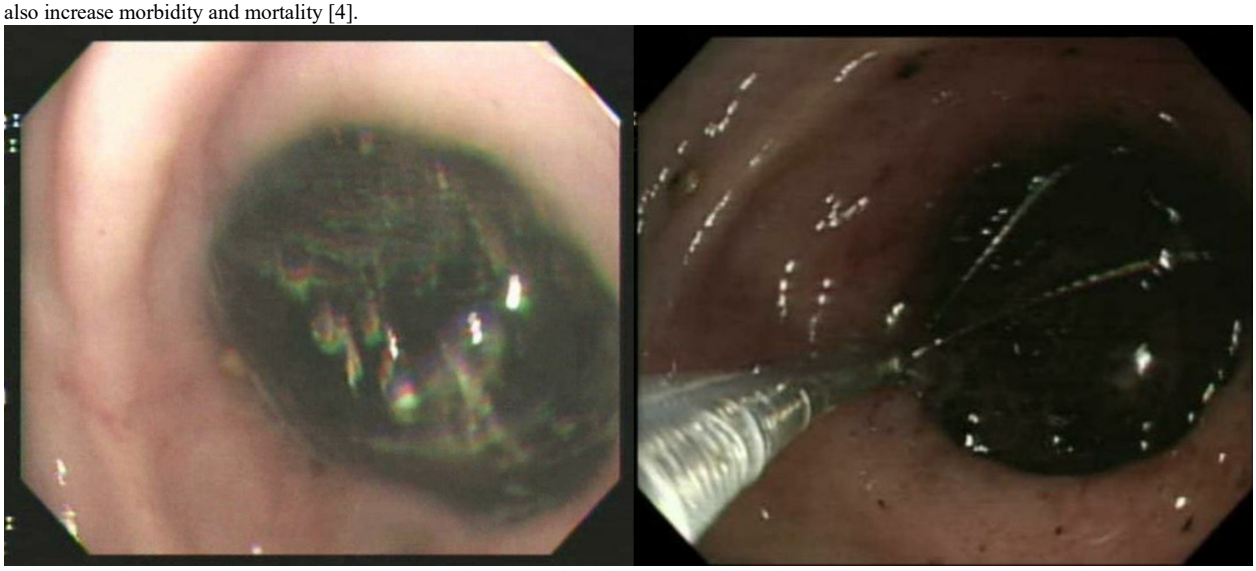

Figure 2: Endoscopic picture showing a large stone obstructing the pyloric ring with a trial to remove it using a Retrieval Basket (Boston Scientific).

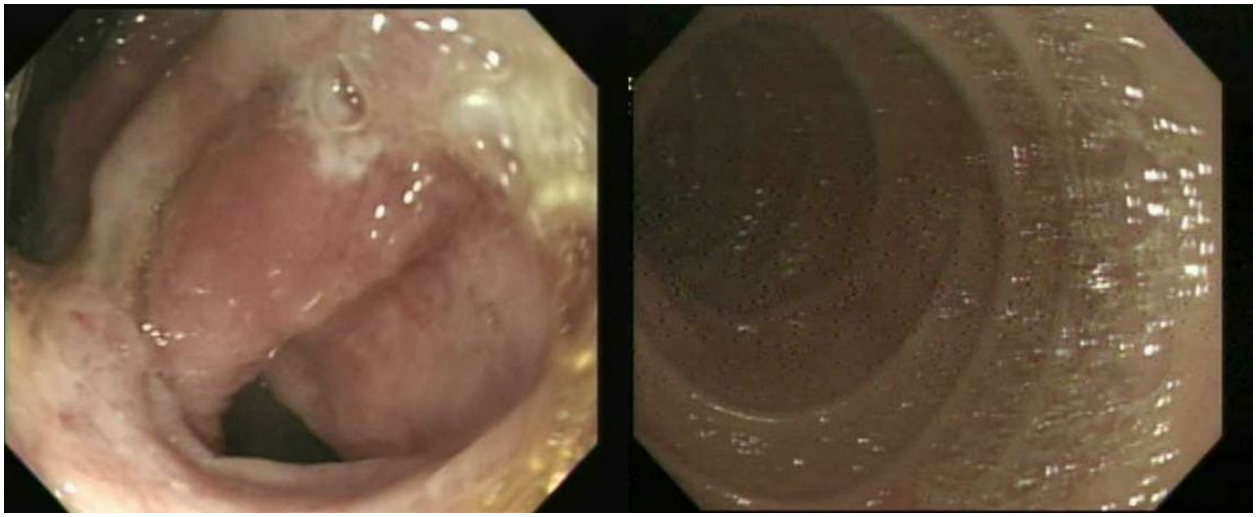

Figure 3: Showing the pyloric ring, duodenal bulb, and second part of the duodenum after the removal of the stone.

Multiple diagnostic modalities can be used in the workup for BS, but CT and EGD are the most widely utilized diagnostic modalities with the highest specificity and sensitivity, (95% and 100% in the former) with EGD being the most commonly used modality in patients presenting with overt bleeding. CT with contrast can also be used in diagnosis with the extravasated contrast outlining the fistula [6].

In our case, Abdominal X-rays followed by CT were sufficient to reach a definitive diagnosis of BS.

In terms of BS management, endoscopy utilization is especially worthwhile in elderly patients with significant comorbidities [7]. However, a study done by Howells et al. showed up to 91% failure of endoscopic and percutaneous extraction despite the availability of expert providers [8]. Nevertheless, a variety of different endoscopic techniques have been shown to be successful [9]. For example, Endoscopic Electrohydraulic Lithotripsy (EHL) has been utilized by Avci et al. to help dissolve a 3 cm biliary stone lodged at the proximal duodenum [10]. In another case, gastric outflow was restored endoscopically in a poor surgical candidate with a pigmented gallstone using Roth Net Platinum Universal Retriever [11].

In case EGD fails, surgery is required. Traditional methods like open gastrotomy, pylorotomy, or duodenotomy are often used but are less preferred due to higher morbidity and mortality rates. Laparoscopy is also used in some cases where open surgery is not an option. For elderly patients who are not suitable candidates for surgery due to increased surgical risks, a two-step procedure is considered. This involves first removing the stone and then performing cholecystectomy and fistula repair [12].

4. Conclusions

In conclusion, using the trapezoid RX wire-guided retrieval basket (Boston Scientific) along with Alliance™ II Inflation Handle for mechanical lithotripsy and the biliary extractor balloon catheter as described in this endoscopic approach to treat BS may improve patient outcomes.

Conflicts of Interest:

None

Ethical Approval:

None

Funding Source:

None

Acknowledgements:

None

Institutional Review Board (IRB) Approval:

None

LLM Statement:

None

Authors Contribution Statement:

MG wrote the case presentation section, case reporter, and provided the endoscopy images. HA reviewed the previous literature, wrote the introduction, extracted some key points, contributed to the discussion writing and corresponding author. AS contributed to the discussion section by describing previous case data. SA Wrote the main discussion part after reviewing the literature, and submission of the article. SH reviewed the manuscript and wrote the abstract. MS Whole paper review, senior author of the paper.

Data Availability Statement:

Full Endoscopic video of the case is available with the author upon request.

References

1. Turner AR, Kudaravalli P, Al-Musawi JH, Ahmad H. Bouveret Syndrome (Bilioduodenal Fistula). StatPearls. Treasure Island (FL): StatPearls Publishing, Copyright © 2023, StatPearls Publishing LLC.; 2024.

2. Dunlop H, Goodarzi MR. Bouveret Syndrome: A Rare Case of Gallstone Ileus Further Complicated by Stone Migration. Cureus. 2020: e11219 [PMID: 33154859 10.7759/cureus.11219: 10.7759/cureus.11219]

3. Qasaimeh GR, Bakkar S, Jadallah K. Bouveret's Syndrome: An Overlooked Diagnosis. A Case Report and Review of Literature. Int Surg. 2014: 819 [PMID: 25437593 10.9738/INTSURG-D-14-00087.1: 10.9738/INTSURG-D-14-00087.1]

4. Probert S, Cai W, Islam F, Ballanamada Appaiah NN, Salih A. Bouveret Syndrome: A Rare Case and Review of the Literature. Cureus. 2022: e24768 [PMID: 35686250 10.7759/cureus.24768: 10.7759/cureus.24768]

5. Yu YB, Song Y, Xu JB, Qi FZ. Bouveret's syndrome: A rare presentation of gastric outlet obstruction. Exp Ther Med. 2019: 1813 [PMID: 30783453 10.3892/etm.2019.7150: 10.3892/etm.2019.7150]

6. Nickel F, Muller-Eschner MM, Chu J, von Tengg-Kobligk H, Muller-Stich BP. Bouveret's syndrome: presentation of two cases with review of the literature and development of a surgical treatment strategy. BMC Surg. 2013: 33 [PMID: 24006869 10.1186/1471-2482-13-33: 10.1186/1471-2482-13-33]

7. Zhao JC, Barrera E, Salabat M, Denham W, Leung D, Ujiki M. Endoscopic treatment for Bouveret syndrome. Surg Endosc. 2013: 655 [PMID: 23052513 10.1007/s00464-012-2533-8: 10.1007/s00464-012-2533-8]

8. L H, L L, M D. Gallstone Coleus: A Rare Relation of Gallstone Ileus. International Journal of Surgery and Research. 2015: 28 10.19070/2379-156x-150006: 10.19070/2379-156x-150006]

9. Puri V, Lee RW, Amirlak BA, Lanspa SJ, Fitzgibbons RJ, Jr. Bouveret syndrome and gallstone ileus. Surg Laparosc Endosc Percutan Tech. 2007: 328 [PMID: 17710061 10.1097/SLE.0b013e31806c7dc2: 10.1097/SLE.0b013e31806c7dc2]

10. Avci A, Gogenur I, Bulut M. Bouveret's syndrome treated with endoscopic electrohydraulic lithotripsy. BMJ Case Rep. 2019: [PMID: 30798279 10.1136/bcr-2018-228316: 10.1136/bcr-2018-228316]

11. Jindal A, Philips CA, Jamwal K, Sarin SK. Use of a Roth Net Platinum Universal Retriever for the endoscopic management of a large symptomatic gallstone causing Bouveret's syndrome. Endoscopy. 2016: E308 [PMID: 27669536 10.1055/s-0042-116430: 10.1055/s-0042-116430]

12. Rey Chaves CE, Villamil CJ, Ruiz S, Galvis V, Conde D, Sabogal Olarte JC. Cholecystogastric fistula in Bouveret syndrome: Case report and literature review. Int J Surg Case Rep. 2022: 106918 [PMID: 35339038 10.1016/j.ijscr.2022.106918: 10.1016/j.ijscr.2022.106918]

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Letter to the Editor

Potential Use of Icosapent Ethyl in the Management of Acute Pancreatitis

Hazem Abosheaishaa [1], Mahmoud Nassar [2]*

1- Internal Medicine Department, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals Queens, NY, USA.
2- Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, New York, USA.

ARTICLE INFO

Article history:
Received 05 Nov. 2024
Received in revised form 17 Dec. 2024
Accepted 20 Dec. 2024

Keywords:
Acute Pancreatitis
Anti-inflammatory Therapy
Eicosapentaenoic Acid
Hypertriglyceridemia
Icosapent Ethyl
Omega-3 Fatty Acids
Vascepa

LETTER TO THE EDITOR

Dear Editor,

We are writing to highlight the potential use of Icosapent Ethyl (Vascepa) as a management option for acute pancreatitis. To the best of my knowledge, a limited number of studies have investigated this use, but it is not yet Food and Drug Administration (FDA) approved for this indication.

Previous studies have suggested that omega-3 fatty acids, such as Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), may have anti-inflammatory properties and could potentially be beneficial in reducing the inflammation and triglyceride levels associated with acute pancreatitis [1]. These mechanisms consist of systemic inflammation reduction by the inhibition of inflammatory mediators since omega-3 fatty acids inhibit the synthesis of pro-inflammatory cytokines such as IL-1β and IL-6 [2]. Moreover, they alter intracellular signaling pathways linked to transcription factors such as nuclear factor-κB, which impacts the expression of genes linked to inflammation [3]. Surprisingly, it helped with inflammation resolution by enhancing the removal of inflammatory cells and promoting the production of certain pro-resolving mediators in mice with pancreatitis [4].

EPA may serve as a valuable dietary supplement for individuals with risk factors for heart disease. It has potential benefits for conditions such as cardiovascular disease, diabetes, obesity, cancer, and stroke. EPA has been shown to lower inflammation, cholesterol, blood pressure, and blood clotting, and improve coronary artery function. Additionally, it can reduce inflammation and enhance body composition, supporting weight loss efforts [5].

A case study reported the use of Icosapent Ethyl as a treatment for severe acute pancreatitis in a 31-year-old male patient with abrupt acute alcoholic pancreatitis, requiring ICU admission, intubation, and mechanical ventilation, renal replacement therapy, and pressors; the patient showed remarkable improvement after initiation of icosapent Ethyl treatment via gastrostomy tube (G-tube) and had a complete recovery [1].

* ***Corresponding author:*** *Hazem Abosheaishaa, Internal Medicine Department, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals Queens, NY, USA. Email Address: mailto: hazemabosheaishaa@gmail.com*

ISSN (Print): 3066-4004, ISSN (Online): 3066-4012 – See front matter

Citation: Abosheaishaa H, Nassar M. Potential Use of Icosapent Ethyl in the Management of Acute Pancreatitis. ASIDE GI. 2025;1(1):5-6. doi:10.71079/ASIDE.GI.0107256

https://doi.org/10.71079/ASIDE.GI.0107256
Journal homepage: https://asidejournals.com/index.php/Gastroenterology

A randomized clinical trial (RCT) by Wang (2008) investigated the impact of omega-3 fatty acid supplementation on inflammation and systemic disease progression in severe acute pancreatitis. 40 patients with severe acute pancreatitis were randomly assigned to receive parenteral nutrition with either soybean oil or fish oil. Results revealed that patients who received fish oil had higher levels of EPA, reduced C-reactive protein (CRP) levels, and improved oxygenation index after five days of treatment. Additionally, the fish oil group had a shorter duration of continuous renal replacement therapy compared to the control group. The study concludes that supplementing parenteral nutrition with omega-3 fatty acids can effectively decrease inflammation, enhance respiratory function, and reduce the need for Continuous Renal Replacement Therapy (CRRT) in severe acute pancreatitis [6].

Currently, treatment options for acute pancreatitis caused by hypertriglyceridemia are limited as there are no FDA-approved options for intractable hyperchylomicronemia. Lifestyle modifications, such as weight loss and dietary intake limitations, are essential in treating patients with hypertriglyceridemia [7].

However, these findings suggest that Vascepa may be a breakthrough therapy for severe acute pancreatitis due to its anti-inflammatory activity and the absence of direct therapy for the disease. More research including RCTs is needed to confirm the safety and efficacy of Vascepa as a management option for acute pancreatitis.

Conflicts of Interest:
None

Ethical Approval:
None

Funding Source:
None

Acknowledgements:
None

Institutional Review Board (IRB) Approval:
None

LLM Statement:
None

Authors Contribution Statement:
All authors have contributed equally to the conception, drafting, review, and final approval of this manuscript. Each author has read and agreed to the final version for publication.

Data Availability Statement:
None

References

1. Berger AA, Sherburne R, Urits I, Patel H, Eskander J. Icosapent Ethyl (Vascepa(R)) for the Treatment of Acute, Severe Pancreatitis. Cureus. 2020: e11551 [PMID: 33365220 10.7759/cureus.11551: 10.7759/cureus.11551]

2. Krupa KN, Fritz K, Parmar M. Omega-3 Fatty Acids. [Updated 2024 Feb 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564314/

3. Surette ME. The science behind dietary omega-3 fatty acids. CMAJ. 2008 Jan 15;178(2):177-80. doi: 10.1503/cmaj.071356. PMID: 18195292; PMCID: PMC2174995.

4. Weylandt KH, Nadolny A, Kahlke L, Köhnke T, Schmöcker C, Wang J, Lauwers GY, Glickman JN, Kang JX. Reduction of inflammation and chronic tissue damage by omega-3 fatty acids in fat-1 transgenic mice with pancreatitis. Biochim Biophys Acta. 2008 Nov;1782(11):634-41. doi: 10.1016/j.bbadis.2008.08.011. Epub 2008 Sep 12. PMID: 18832028; PMCID: PMC2614880.

5. Nassar M, Jaffery A, Ibrahim B, Baraka B, Abosheaishaa H. The multidimensional benefits of eicosapentaenoic acid: from heart health to inflammatory control. The Egyptian Journal of Internal Medicine. 2023: 81 10.1186/s43162-023-00265-6: 10.1186/s43162-023-00265-6]

6. Wang X, Li W, Li N, Li J. Omega-3 fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. JPEN J Parenter Enteral Nutr. 2008: 236 [PMID: 18443134 10.1177/0148607108316189: 10.1177/0148607108316189]

7. Guerriero T, James CS. A rare case of severe hypertriglyceridemia in a patient with no acute pancreatitis after previous bouts of pancreatitis secondary to hypertriglyceridemia. Journal of Clinical and Translational Endocrinology: Case Reports. 2022: 100102 10.1016/j.jecr.2021.100102: 10.1016/j.jecr.2021.100102]

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Original Article

Dexmedetomidine as an Adjunctive Sedative in Patients Undergoing Endoscopic Submucosal Dissection: A Systematic Review and Meta-Analysis

Hazem Abosheaishaa[1], Abdallfatah Abdallfatah[2], Abdelmalek Abdelghany[2], Arshia Sethi[1], Abdellatif Ismail[3], Doha Mohamed[2], Moataz Aboeldahb[4], Omar Abdelhalim[1], Islam Mohamed[5], Ahmed Y. Azzam[6], Muhammed Amir Essibayi[7], David J. Altschul[7], Mahmoud Nassar[8], Mohammad Bilal[9]*

1- Department of Internal Medicine, Icahn School of Medicine at Mount Sinai / NYC Health + Hospitals Queens, NY, USA.
2- Faculty of Medicine, October 6 University, Giza, Egypt.
3- University of Maryland Medical Center Midtown Campus, Baltimore, MD, USA.
4- Mayo Clinic Gastroenterology and Hepatology, Rochester, MN, USA
5- Department of Gastroenterology, University of Missouri, Columbia, MO, USA
6- Montefiore-Einstein Cerebrovascular Research Lab, Albert Einstein College of Medicine, Bronx, NY, USA.
7- Department of Neurological Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.
8- Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, NY USA.
9- Division of Gastroenterology and Hepatology, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA.

ARTICLE INFO

Article history:
Received 11 Nov. 2024
Received in revised form 26 Nov. 2024
Accepted 15 Dec. 2024

Keywords:
Endoscopic Submucosal Dissection
ESD
Dexmedetomidine
Precedex
Systematic Review
Meta-Analysis

ABSTRACT

Introduction: Endoscopic submucosal dissection (ESD) is a technique for removing dysplastic lesions in the gastrointestinal tract but carries risks like pain and perforation. Dexmedetomidine, an α2-receptor agonist, offers potential benefits as an adjunct sedative during ESD by providing anxiolysis and analgesia. This systematic review and meta-analysis assesses its efficacy and safety.
Methodology: We searched databases including Embase, Medline/PubMed, Scopus, and Web of Science up to April 21, 2024, following PRISMA guidelines. Eligible studies used dexmedetomidine with other sedatives for ESD. We analyzed outcomes such as en-bloc and complete resection rates, sedation duration, and adverse events, using RevMan for meta-analysis with a random-effects model.
Results: The initial search retrieved 216 studies and after screening, eight studies were included in the final analysis. Dexmedetomidine showed no significant difference in en-bloc or complete resection rates compared to controls. Sedation and procedure times were similar between the two groups as well. Dexmedetomidine significantly reduced restlessness (OR 0.15, 95% CI:0.07 to 0.29) and increased bradycardia (OR 7.15, 95% CI 3.17 to 16.11) compared to controls. Upon subgroup analysis, Dexmedetomidine plus Propofol, and Dexmedetomidine plus Midazolam, revealed the same findings regarding restlessness and bradycardia compared to controls which confirmed the adjunctive effects of Dexmedetomidine.
Conclusion: Dexmedetomidine as an adjunctive sedative appears safe and effective in ESD, reducing restlessness without significant adverse events. The risk of bradycardia is increased, which may be reflective of reduced physiological stress. Future studies should explore optimal dosing and compare Dexmedetomidine with other sedatives in diverse populations.

1. Introduction

Endoscopic tumor resection is one of the most common modalities in GI tumor management. Endoscopic submucosal dissection (ESD) is considered superior to mucosal resection in view of offering complete resection with negative histological margins irrespective of the size of the original lesion [1]. Despite these overwhelming advantages, ESD is associated with multiple postoperative complications including bleeding, postoperative perforation, and minor complications like abdominal pain, nausea, vomiting, and stricture which limits its use [2]. Post-operative abdominal pain is a debilitating complication associated with ESD which is severely underestimated and results in decreased patient satisfaction and longer hospital stays. Studies show the incidence of postoperative pain in 44.9~62.8% of patients, especially in the early

* ***Corresponding author:*** *Hazem Abosheaishaa, Internal Medicine Department, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals Queens, NY, USA. Email Address: hazemabosheaishaa@gmail.com.*

ISSN (Print): 3066-4004, ISSN (Online): 3066-4012 – See front matter

Citation: Abosheaishaa H, Abdallfatah A, Abdelghany A, et al. Dexmedetomidine as an Adjunctive Sedative in Patients Undergoing Endoscopic Submucosal Dissection: A Systematic Review and Meta-Analysis. ASIDE GI. 2025;1(1):7-14. doi:10.71079/ASIDE.GI.0109257.

https://doi.org/10.71079/ASIDE.GI.0109257
Journal homepage: https://asidejournals.com/index.php/Gastroenterology

post-operative period necessitating the use of aggressive pain management [3, 4]. Dexmedetomidine is a new α2-receptor agonist that has anxiolytic, sedative, and analgesic properties which when used in combination with other anesthetics help lower their dose and also decrease postoperative opioid consumption and pain intensity [5, 6]. A study done by Chang et al., also shows a better cardiovascular profile of dexmedetomidine as compared to propofol [7]. In our study, we reviewed the possible benefits of dexmedetomidine as an adjunct sedative perioperatively in patients undergoing ESD for GI adenomas and early-stage neoplastic lesions. We evaluated its efficacy by assessing variables like en-bloc resection, Complete resection, sedation time, procedure time, patient restlessness, and other adverse events.

2. Methodology:

2.1. Search Strategy and Data Extraction:

A systematic search of relevant literature was conducted across multiple databases, including Embase, Scopus, Web of Science, Medline/PubMed, and Cochrane, from their inception to February 28, 2024. The search strategy utilized Boolean operators to combine terms related to the population, intervention, and outcomes of interest. The following search strategy was employed: ("endoscopic submucosal dissection" OR "ESD" OR "submucosal dissection") AND ("dexmedetomidine" OR "dexmedetomidine" OR "sedative") (Table 1). The search strategy aimed to identify studies investigating the use of dexmedetomidine as an adjunctive sedative in endoscopic submucosal dissection procedures. Our research adhered to the recommended guidelines for reporting systematic reviews and meta-analyses. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and Cochrane criteria were followed to ensure transparency and completeness in reporting [8, 9].

Two independent reviewers screened titles, abstracts, and full-text articles for inclusion based on predefined eligibility criteria. Any disagreements were resolved through discussion or consultation with a third reviewer. Data extraction was conducted independently by two co-authors using a standardized data extraction form, with discrepancies resolved through consensus. Extracted data included study characteristics, patient demographics, details of the intervention and comparator, and outcomes of interest.

2.2. Inclusion Criteria and Study Outcomes:

Studies eligible for inclusion in this meta-analysis were those focusing on patients who had gastrointestinal adenomas and early-stage neoplastic lesions eligible for endoscopic submucosal dissection (ESD) treatment. The intervention of interest was the use of dexmedetomidine as an adjunctive medication in combination with other sedatives in submucosal endoscopic dissection. There was no specific comparator for this review. The primary outcome of interest was the en-bloc resection (successful removal of the entirety of a tumor without violation of its capsule). Secondary outcomes included Complete resection (excision of all affected tissue, including the tumor and a healthy surrounding tissue) sedative time (duration during which a sedative medication exerts its effects on a patient in minutes) procedure time (total duration taken to complete the surgery), restlessness(inability to remain still), and different adverse events(eg. Hypoxia, Brady cardia, Hypotension, Perforation and bleeding). Included study designs were randomized controlled trials (RCTs) and observational studies if applicable. Studies not written in English or with inadequate translation, Systematic reviews, Meta-analyses, Case reports, editorials, letters, or conference abstracts without full-text availability, animal studies, or studies conducted on non-human subjects were excluded.

2.3. Risk of Bias Assessment:

The risk of bias and methodological quality of the included studies was assessed independently by two authors. The Cochrane risk-of-bias tool version 2, (ROB 2) was employed for RCTs. For observational studies, we used the Newcastle-Ottawa Scale, any discrepancies were resolved through discussion or consultation with a third reviewer [10].

2.4. Statistical Analysis:

A meta-analysis was conducted using Review Manager 5.4 (Cochrane Collaboration, Copenhagen, The Nordic Cochrane Centre). Given the anticipated heterogeneity in study designs and populations, a random-effects model was utilized. Summary measures were expressed as pooled odds ratios (OR) with corresponding 95% confidence intervals (CI) for proportional variables and mean differences with corresponding 95% CIs for continuous variables. Statistical significance was set at a p-value <0.05. Heterogeneity was assessed using the I2 statistic, with an I2 value of ≥50% indicating significant heterogeneity defined by the Cochrane Handbook for systematic reviews [11].

3. Results

3.1. Search results:

The initial search retrieved 216 studies, 105 duplicates removed automatically with covidence, and 7 duplicates removed manually. The remaining 104 underwent title and abstract screening, and 25 full texts were assessed for inclusion. Eight studies [3,18-20,24-25,28-29] were included in our final analysis (Figure 1).

3.2. Study and patient characteristics:

A total of 836 patients were included in our meta-analysis. Of the 836 patients, 412 (49.2%) were assigned to the Dexmedetomidine group, whereas 424 (50.7%) were assigned to the placebo group. The included eight studies' characteristics are displayed in (Table 2).

3.3. Quality of included studies:

Quality assessment of included studies was assessed using (the Cochrane RoB 2 tool) for Randomized clinical trials. Four studies had a total low risk of bias, and one study had a moderate risk of bias. Another three Cohort studies were assessed using the Newcastle–Ottawa Scale with a low risk of bias (Table 3).

3.4. Meta-analysis outcomes:

3.4.1. En-bloc resection

The data from 7 studies were analyzed for En-bloc resection, the odds ratio was 1.45 with a 95% CI of 0.47 to 4.41 which revealed no significant difference between the two groups (p=0.52) at random effect as shown in (Figure 2).

3.4.2. Complete resection:

Three studies reported a complete resection rate, and the odds ratio was 0.62 with a 95% CI of 0.21 to 1.80 which revealed no significant difference between the two groups (p=0.38) as shown in (Figure 3).

3.4.3. Sedation time:

The pooled results from four studies reporting on sedation time revealed that there was no significant difference between the two groups, as shown in Figure 4 (Mean Difference (MD): 7.36, 95% CI: -1.42 to 16.15; I^2 0%; P=0.10).

3.4.4. Procedure Time:

Five studies reporting on procedure time revealed that there was no significant difference between the two groups as shown in Table. 3 (MD: 3.21, 95% CI: -6.32-12.74; I^2 0%; P=0.51).

3.4.5. Restlessness:

Four studies reported a restlessness rate, the odds ratio was 0.15 with a 95% CI of 0.07 to 0.29 which revealed a significant difference between the two groups (p<0.00001). as shown in (Table. 4).

3.4.6. Bradycardia:

Seven studies reported the bradycardia rate. The odds ratio was 7.15 with a 95% CI of 3.17 to 16.11 which revealed a significant difference between the two groups (p<0.00001) as shown in (Table. 4).

3.4.7. Hypoxia:

Four studies reported the Hypoxia rate. The odds ratio was 0.95 with a 95% CI of 0.38 to 2.36 which revealed no significant difference between the two groups (p=0.91) as shown in (Table 4).

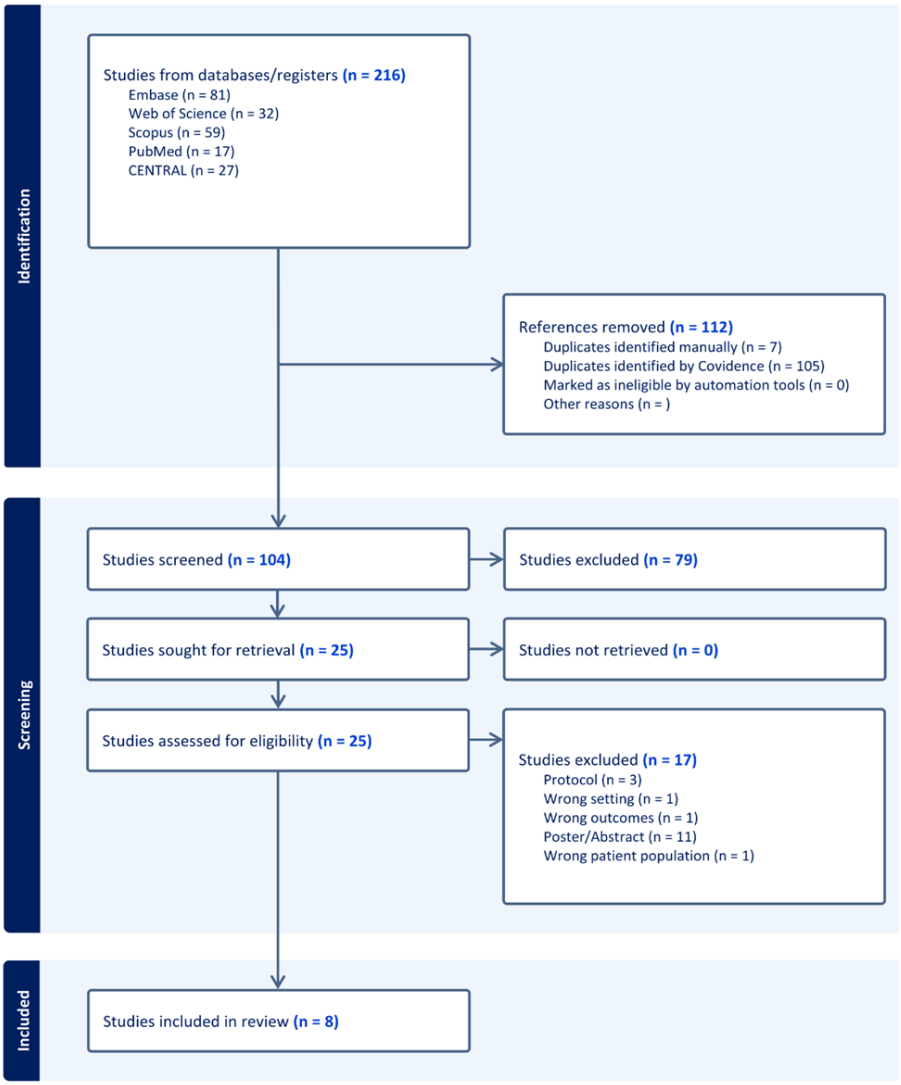

Figure 1: Flowchart of Study Selection Process for Systematic Review.

Table 1: Search strategy:

Database	Search Terms	Search Field	Search Results
Medline	("endoscopic submucosal dissection" OR "ESD" OR "endoscopic dissection") AND ("dexmedetomidine" OR "Dexmedetomidine Hydrochloride" OR “Precedex” OR "MPV-1440" OR "MPV 1440" OR "MPV1440").	All Field	17
Cochrane	("endoscopic submucosal dissection" OR "ESD" OR "endoscopic dissection") AND ("dexmedetomidine" OR "Dexmedetomidine Hydrochloride" OR "MPV-1440" OR "MPV 1440" OR "MPV1440")	All Text	27
WOS	((ALL= (((endoscopic submucosal dissection OR ESD OR endoscopic dissection)))) AND ALL= (((Dexmedetomidine OR Dexmedetomidine Hydrochloride OR MPV-1440 OR MPV 1440 OR MPV1440))))).	All Fields	32
SCOPUS	("endoscopic submucosal dissection" OR "ESD" OR "endoscopic dissection") AND ("dexmedetomidine" OR "Dexmedetomidine Hydrochloride" OR "MPV-1440" OR "MPV 1440" OR "MPV1440").	Title, Abstract, Keywords	59
EMBASE	Embase: ("endoscopic submucosal dissection" OR "ESD" OR "endoscopic dissection") AND ("dexmedetomidine" OR "Dexmedetomidine Hydrochloride" OR "MPV-1440" OR "MPV 1440" OR "MPV1440").	All Field	81

ESD: Endoscopic Submucosal Dissection; WOS: Web of Science

Table 2: baseline characteristics of included studies

Author	Country	Study design	Age means (SD)		Intervention(t/control)	Procedure location	Size of lesion mean (SD)	
			Cases control				Cases	Control
Ashikari 2021 [24]	Japan	RCT	21.25 (8.29)	22.97 (12.78)	propofol plus DEX; propofol alone.	Superficial esophageal cancers	68.86 (30.99)	8 (24.24)
Iwagami 2023 [27]	Japan	Retrospective	NA	NA	MDZ and pethidine hydrochloride + DEX; MDZ and pethidine hydrochloride	Colorectal lesions	64.4(38.2)	85 (55)
Kim 2015 [14]	Korea	RCT	62.8 (8.5)	65.1 (10.2)	DEX- remifentanil; propofol-remifentanil	Esophagus	62.9 (12.3)	10 (34.5)
Kinugasa 2018 [28]	Japan	RCT	22.4 (4.3)	22.5 (2.77)	DEX + Pethidine; Pethidine	Colorectal	67.9 (33.8)	21 (52%)
Lee 2015 [18]	Korea	RCT	23.79 (2.70)	24.32 (2.07)	DEX with on-demand MDZ; MDZ alone	Gastric Tumor	15	22.5
Luo 2023 [3]	China	RCT	57 (7)	55.8 (7.5)	DEX bolus + maintenance intraop; Normal saline	Stomach - gastric	3.4 (1.2)	2.8 (1.3)
Nonaka 2016 [19]	Japan	Retrospective	66.3 (7.7)	68.4 (8.5)	Combination of propofol and DEX; Benzodiazepines	Esophagus	40.1 (12)	40.8 (15.2)
Yoshio 2019 [17]	Japan	Prospective confirmatory single arm	67.7 (5.7)	N/A	Bolus MDZ and pethidine + DEX infusion; MDZ and pethidine boluses	Esophagus	17.3 (8.5)	N/A

SD: Standard Deviation; RCT: Randomized Controlled Trial; DEX: Dexmedetomidine; MDZ: Midazolam; NA: Not Available; intraop: Intraoperative.

Table 3: Risk of bias assessment for included studies.

Author name, year	Study design	Tool used	Overall, ROB
Ashikari, 2021 [24]	RCT	Cochrane RoB 2	Low
Iwagami, 2023 [27]	Cohort	Newcastle–Ottawa Scale	Low
Kim, 2015 [14]	RCT	Cochrane RoB 2	Low
Kinugasa, 2018 [28]	RCT	Cochrane RoB 2	Low
Lee, 2015 [18]	RCT	Cochrane RoB 2	Low
Luo, 2023 [3]	RCT	Cochrane RoB 2	Moderate
Nonaka, 2016 [19]	Cohort	Newcastle–Ottawa Scale	Low
Yoshio, 2019 [17]	Cohort	Newcastle–Ottawa Scale	Moderate

RCT: Randomized Controlled Trial; ROB: Risk of Bias.

Table 4. Outcomes summary

Subgroup	Outcome	Odds Ratio / Mean Difference (95% CI)	P-value
General	Procedure time	3.21 (-6.32 to 12.74)	0.51
	Restlessness	0.15 (0.07 to 0.29)	<0.00001
	Bradycardia	7.15 (3.17 to 16.11)	<0.00001
	Hypoxia	0.95 (0.38 to 2.36)	0.91
	Hypotension	2.73 (0.79 to 9.43)	0.11
	Perforation	0.51 (0.05 to 5.44)	0.58
	Bleeding	0.41 (0.12 to 1.39)	0.15
Dexmedetomidine plus Propofol	En-bloc resection	3.09 (0.12 to 78.70)	0.49
	Complete resection	0.72 (0.23 to 2.24)	0.57
	Procedure time	-4.05 (-27.57 to 19.47)	0.74
	Restlessness	0.14 (0.05 to 0.45)	0.0009
	Bradycardia	10.04 (2.92 to 34.54)	0.0003
	Hypoxia	0.28 (0.11 to 0.71)	0.007
	Hypotension	3.83 (1.00 to 14.69)	0.05
Dexmedetomidine plus Midazolam	En-bloc resection	1.80 (0.50 to 6.51)	0.37
	Restlessness	0.15 (0.06 to 0.35)	<0.0001
	Bradycardia	14.97 (2.44 to 91.68)	0.003
	Hypoxia	0.80 (0.33 to 1.94)	0.62
	Bleeding	0.42 (0.11 to 1.60)	0.20
	Perforation	0.24 (0.01 to 4.13)	0.32

3.4.8. Hypotension:
Seven studies reported the Hypotension rate. The odds ratio was 2.73 with a 95% CI of 0.79 to 9.43 which revealed no significant difference between the two groups (p=0.11) as shown in (Table 4).

3.4.9. Perforation:
Five studies reported the perforation rate. The odds ratio was 0.51 with a 95% CI of 0.05 to 5.44 which revealed no significant difference between the two groups (p=0.58) as shown in (Table 4).

3.4.10. Bleeding:
Three studies reported the Bleeding rate, the odds ratio was 0.41 with a 95% CI of 0.12 to 1.39 which revealed no significant difference between the two groups (p=0.15) as shown in (Table 4).

3.5. Subgroup Analysis Outcomes:

3.5.1. Dexmedetomidine plus Propofol

3.5.1.1. En-bloc resection:
Two studies reported en-bloc resection rate for Dexmedetomidine in combination with propofol, the odds ratio was 3.09 with a 95% CI of 0.12 to 78.70 which revealed no significant difference between the two groups (p=0.49) as shown in (Table 4).

3.5.1.2. Complete resection:
Two studies reported a complete resection rate for Dexmedetomidine in combination with propofol, the odds ratio was 0.72 with a 95% CI of .23 to 2,24 which revealed no significant difference between the two groups (p=0.57) as shown in (Table 4).

3.5.1.3. Procedure Time:
Two studies reporting on procedure time for Dexmedetomidine in combination with propofol revealed that there was no significant difference between the two groups as shown in Table. 3 (MD: -4.05, 95% CI: -27.57-19.47; I^2=63%; P=0.74).

3.5.1.4. Restlessness:
Two studies reported Restlessness for Dexmedetomidine in combination with propofol, the odds ratio was 0.14 with a 95% CI of 0.05 to 0.45 which revealed a significant difference between the two groups (p=0.0009) as shown in (Table 4).

3.5.1.5. Bradycardia:
Two studies reported Bradycardia for Dexmedetomidine in combination with propofol, the odds ratio was 10.04 with a 95% CI of 2.92 to 34.54 which revealed a significant difference between the two groups (p=0.0003) as shown in (Table 4).

3.5.1.6. Hypoxemia:
Two studies reported hypoxemia for Dexmedetomidine in combination with propofol, the odds ratio was 0.28 with a 95% CI of 0.11 to 0.71 which revealed a significant difference between the two groups (p=0.007) as shown in (Table 4).

3.5.1.7. Hypotension:
Two studies reported Hypotension for Dexmedetomidine in combination with propofol, the odds ratio was 3.83 with a 95% CI of 1.00 to 14.69 which revealed a significant difference between the two groups (p=0.05) as shown in (Table 4).

3.5.2. Dexmedetomidine plus Midazolam

3.5.2.1. En-bloc resection:
Two studies reported en-bloc resection for Dexmedetomidine in combination with Midazolam, the odds ratio was 1.80 with a 95% CI of 0.50 to 6.51 which revealed no significant difference between the two groups (p=0.37) as shown in (Table 4).

3.5.2.2. Restlessness:
Two studies reported Restlessness for Dexmedetomidine in combination with Midazolam, the odds ratio was 0.15 with a 95% CI of 0.06 to 0.35 which revealed a significant difference between the two groups ($p < 0.0001$) as shown in (Table 4).

3.5.2.3. Bradycardia:
Two studies reported Bradycardia for Dexmedetomidine in combination with Midazolam, the odds ratio was 14.97 with a 95% CI of 2.44 to 91.68 which revealed a significant difference between the two groups (p=0.003) as shown in (Table 4).

3.5.2.4. Hypoxia:
Two studies reported Hypoxia for Dexmedetomidine in combination with Midazolam, the odds ratio was 0.80 with a 95% CI of 0.33 to 1.94 which revealed no significant difference between the two groups (p=0.62) as shown in (Table 4).

3.5.2.5. Bleeding:
Two studies reported Bleeding for Dexmedetomidine in combination with Midazolam, the odds ratio was 0.42 with a 95% CI of 0.11 to 1.60 which revealed no significant difference between the two groups (p=0.20) as shown in (Table 4).

3.5.2.6. Perforation:
Two studies reported Perforation for Dexmedetomidine in combination with Midazolam, the odds ratio was 0.24 with a 95% CI of 0.01 to 4.13 which revealed no significant difference between the two groups (p=0.32) as shown in (Table 4).

4. Discussion

Although the debilitating pain associated with ESD warrants aggressive pain management, physicians are hesitant due to the possibility of masking the pain of perforation. This not only causes patient discomfort but also increases the burden on healthcare by prolonging discharge time [2, 4]. A study done by Seiichiro et al. shows an increased incidence of metachronous gastric cancer in patients who underwent curative ESD of early gastric cancer [12]. These warrant further endoscopic surveillance and possible repeat ESD. However, poorly managed post-operative pain increases apprehension in patients for further endoscopic procedures. As previously described, a few studies have been done describing the incidence of postoperative pain after ESD but there is no consensus on the management of the said pain. Studies done by Lee and Kim recommend a single dose of dexamethasone or postoperative local bupivacaine and triamcinolone [13, 14].

In our study, we found a significant reduction in restlessness and bradycardia associated with dexmedetomidine highlighting its potential as an effective sedative agent for endoscopic procedures. A study that investigated the effect of local anesthesia in ESD procedures showed that local anesthesia decreased the incidence of bradycardia (OR = 0.16, 95% CI = 0.03, 0.95) [15]. We also observed a statistically significant decrease in tachycardia which could indicate less anxiety and pain thus providing a more comfortable sedative experience for the patients. These properties could be attributed to its selective alpha 2 adrenergic agonist and sympatholytic properties [15].

The non-significant difference found in en bloc resection rates between dexmedetomidine, and the comparator groups alleviated concerns regarding the influence of the sedation regimen on the technical aspects of the procedure [16].

The subgroup analysis also revealed better outcomes particularly in terms of reduced restlessness and bradycardia, with Dexmedetomidine in combination with Midazolam compared to other combinations. The anxiolytic and amnestic properties of Midazolam, coupled with the sedative and analgesic effects of Dexmedetomidine, may offer superior patient comfort and procedural tolerance. Additionally, considering the favorable safety profile of Midazolam in terms of respiratory depression compared to Propofol, this combination presents a compelling option for optimizing sedation strategies in endoscopic settings [17].

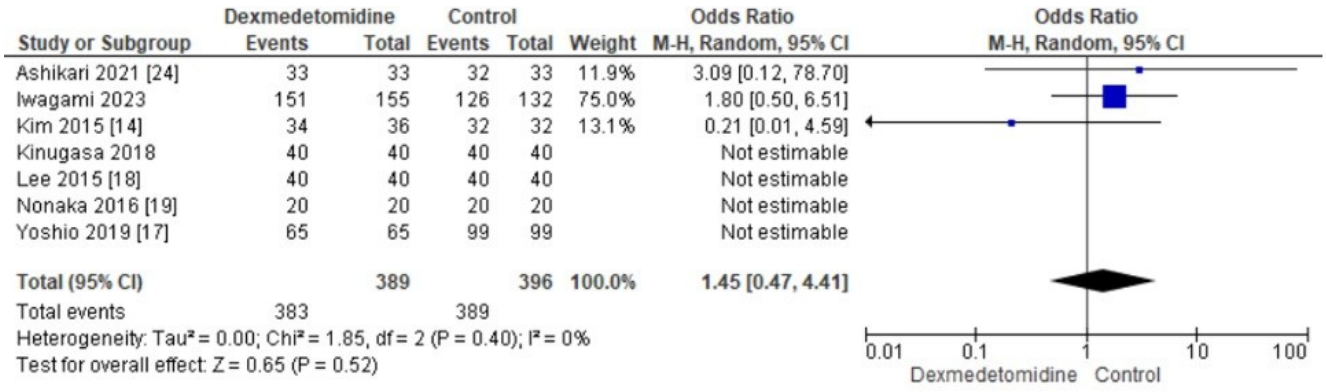

Figure 2: Forest Plot illustrating the Odds Ratios of Dexmedetomidine to control for En-bloc resection rates

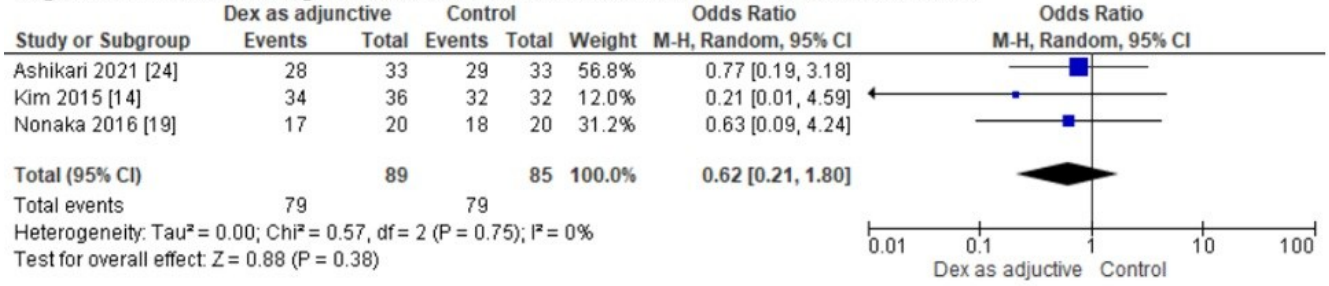

Figure 3: Forest Plot illustrating the Odds Ratios of Dexmedetomidine to Control for complete resection rates

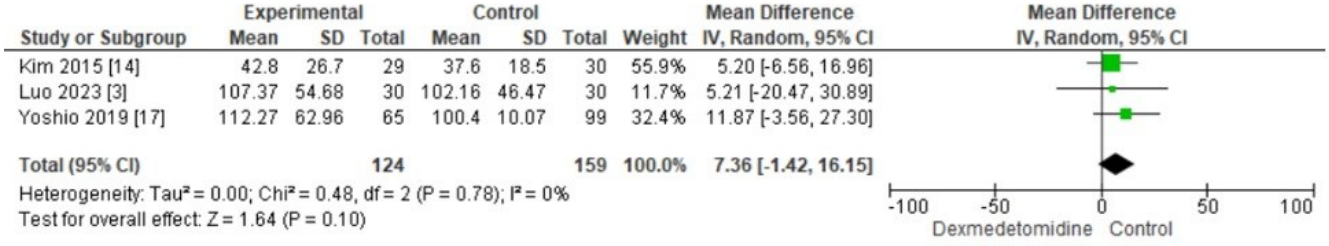

Figure 4: Forest Plot illustrating the Odds Ratios of Dexmedetomidine to Control for sedation time

Our review suggests that dexmedetomidine is an effective sedative agent for ESD. Lee et al. [18] on the other hand, compared the outcomes of sedation using dexmedetomidine infusion plus on-demand midazolam versus sedation using midazolam infusion plus on-demand midazolam. They concluded that the sedation effect of dexmedetomidine with midazolam was superior to the sedation effect with midazolam alone. Furthermore, four studies reported sedation time as an outcome, while five studies reported procedure time as an outcome, (Table 4). The pooled results from these studies showed no statistically significant difference in sedation or procedure time between the dexmedetomidine and the control group. Despite the significant reduction in intraoperative restlessness in the dexmedetomidine group in our review, as mentioned above, this did not translate into a shorter sedation or procedure time (Table 4).

Nonaka et al. [19] reported a significantly shorter procedure time in the combination group (dexmedetomidine and propofol) compared to the benzodiazepine group; nevertheless, this finding was lost after pooling with other studies in the analysis, as shown in (Table 4).

In terms of safety, our findings support the use of dexmedetomidine as an adjunctive agent in procedural sedation for ESD procedures, consistent with previous studies [20, 21]. As noted by Candiotti et al. [20], the Dexmedetomidine group demonstrated a higher incidence of bradycardia. However, there was no statistically significant increase in the occurrence of other adverse events such as hypoxia, hypotension, bleeding, or perforation. Additionally, Dexmedetomidine's cardiovascular and hemodynamic effects are well-known and are attributed to its strong alpha 2-adrenergic agonist effect and include bradycardia, hypotension, and hypoxia [20-23]. Kim et al. evaluated risk factors for dexmedetomidine-associated bradycardia during spinal anesthesia [23] and found that a long tourniquet time and low baseline heart rate were associated with an increased incidence of bradycardia during procedures under spinal anesthesia. Notably, Alshikaria et al. [24] reported that no serious adverse events were observed in patients in the dexmedetomidine group who experienced bradycardia and that their clinical outcomes were not altered due to it, which is also consistent with previous literature [25, 26].

The use of Dexmedetomidine as an adjunctive sedative has shown promising results in our meta-analysis, yet this type of intervention needs further exploration. The included studies in this review have already explored the combination of Dexmedetomidine with the two main sedatives, propofol and midazolam. The results are extraordinary in terms of restlessness and bradycardia incidence, the latter being a good sign of less stress and discomfort during the procedure. Less movements (restlessness) during the ESD procedure leads to more convenient and accurate procedures from the operator. So, this therapy should be explored more to reach the best results possible for the patient.

More exploration means more multicenter randomized controlled trials and observational studies comparing this type of adjunctive therapy with

other adjunctive sedatives and even other types of pain management methods, like local anesthesia in the region of intervention, to test this intervention's safety and efficacy to standardize its use during ESD procedures in the near future.

Limitations: To our knowledge, this is the first meta-analysis to assess the safety and efficacy of Dexmedetomidine as an adjunctive sedative after ESD. Additionally, we performed subgroup analysis according to each general therapy. Most included articles (6 out of 8) did not conduct a head-to-head comparison between dexmedetomidine and other agents. Also, the limited number of published clinical trials and the number of patients included in certain subgroups make our evidence and conclusions limited on some outcomes. All of our eight included trials were conducted in eastern Asia, including 5 in Japan, two in Korea, and one in China. Thus, the generalizability of this study results to other regions with different ethnicities and medical environments may be affected. A standardized dosage of dexmedetomidine as an adjuvant sedative has not yet been established, resulting in a wide variety of dexmedetomidine regimens.

5. Conclusion

In conclusion, our meta-analysis supports the safe use of dexmedetomidine as an adjunctive sedative in ESD procedures. Dexmedetomidine, when combined with other sedatives, appears to reduce restlessness without increasing the risk of hypoxia, hypotension, bleeding, or perforation. The increased risk of bradycardia noted with dexmedetomidine can be perceived as less physiological stress and tachycardia during procedures. However, our findings are limited by the lack of direct comparisons with other sedatives and the predominantly Eastern Asian study populations. Further research, including multicenter trials, is needed to establish optimal dosing regimens and evaluate dexmedetomidine's efficacy compared to other sedatives and pain management methods in diverse patient populations.

Conflicts of Interest:

None

Ethical Approval:

None

Funding Source:

The project described was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through CTSA award number: UM1TR004400. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Acknowledgements:

None

Institutional Review Board (IRB) Approval:

None

LLM Statement:

None

Authors Contribution Statement:

H.A., A.A., A.A., A.S., A.I., D.M., M.A., O.A., I.M., A.Y.A., M.N., and M.B. equally contributed to the conception, design, data acquisition, analysis, and interpretation of this research. All authors were involved in drafting the manuscript and revising it critically for important intellectual content. They have also given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement:

All data generated or analyzed during this study are included in this published article. The data are publicly available and have been cited appropriately within the text of the document.

References

1. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut. 2009: 331 [PMID: 19001058 https://doi.org/10.1136/gut.2008.165381]

2. Nishizawa T, Yahagi N. Endoscopic mucosal resection and endoscopic submucosal dissection: technique and new directions. Curr Opin Gastroenterol. 2017: 315 [PMID: 28704212 https://doi.org/10.1097/MOG.0000000000000388]

3. Luo X, An LX, Chen PS, Chang XL, Li Y. Efficacy of dexmedetomidine on postoperative pain in patients undergoing gastric and esophageal endoscopic submucosal dissection: a study protocol for a randomized controlled prospective trial. Trials. 2022: 491 [PMID: 35698203 https://doi.org/10.1186/s13063-022-06432-4]

4. Kim JW, Jang JY, Park YM, Shim JJ, Chang YW. Clinicopathological characteristics of patients with pain after endoscopic submucosal dissection for gastric epithelial neoplasm. Surg Endosc. 2019: 794 [PMID: 30014330 https://doi.org/10.1007/s00464-018-6345-3]

5. Ramsay MA, Luterman DL. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology. 2004: 787 [PMID: 15329604 https://doi.org/10.1097/00000542-200409000-00028]

6. Liu Y, Liang F, Liu X, Shao X, Jiang N, Gan X. Dexmedetomidine Reduces Perioperative Opioid Consumption and Postoperative Pain Intensity in Neurosurgery: A Meta-analysis. J Neurosurg Anesthesiol. 2018: 146 [PMID: 28079737 https://doi.org/10.1097/ANA.0000000000000403]

7. Chang ET, Certal V, Song SA, Zaghi S, Carrasco-Llatas M, Torre C, Capasso R, Camacho M. Dexmedetomidine versus propofol during drug-induced sleep endoscopy and sedation: a systematic review. Sleep Breath. 2017: 727 [PMID: 28130737 https://doi.org/10.1007/s11325-017-1465-x]

8. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010: 336 [PMID: 20171303 https://doi.org/10.1016/j.ijsu.2010.02.007]

9. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019: ED000142 [PMID: 31643080 https://doi.org/10.1002/14651858.ED000142]

10. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019: l4898 [PMID: 31462531 https://doi.org/10.1136/bmj.l4898]

11. Deeks JJ, Bossuyt PM, Leeflang MM, Takwoingi Y (editors). Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Version 2.0 (updated July 2023). Cochrane, 2023. Available from https://training.cochrane.org/handbook-diagnostic-test-accuracy/current

12. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Nakajima T, Sekiguchi M, Mori G, Taniguchi H, Sekine S, Katai H, Saito Y. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy. 2015: 1113 [PMID: 26165734 https://doi.org/10.1055/s-0034-1392484]

13. Lee HW, Lee H, Chung H, Park JC, Shin SK, Lee SK, Lee YC, Hong JH, Kim DW. The efficacy of single-dose postoperative intravenous dexamethasone for pain relief after endoscopic submucosal dissection for gastric neoplasm. Surg Endosc. 2014: 2334 [PMID: 24570015 https://doi.org/10.1007/s00464-014-3463-4]

14. Kim B, Lee H, Chung H, Park JC, Shin SK, Lee SK, Lee YC. The efficacy of topical bupivacaine and triamcinolone acetonide injection in the relief of pain after endoscopic submucosal dissection for gastric neoplasia: a randomized double-blind, placebo-controlled trial. Surg Endosc. 2015: 714 [PMID: 25060683 https://doi.org/10.1007/s00464-014-3730-4]

15. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. Rev Bras Anestesiol. 2012: 118 [PMID: 22248773 https://doi.org/10.1016/S0034-7094(12)70110-1]

16. Dumoulin FL, Hildenbrand R. Endoscopic resection techniques for colorectal neoplasia: Current developments. World J Gastroenterol. 2019: 300 [PMID: 30686899 https://doi.org/10.3748/wjg.v25.i3.300]

17. Yoshio T, Ishiyama A, Tsuchida T, Yoshimizu S, Horiuchi Y, Omae M, Hirasawa T, Yamamoto Y, Sano H, Yokota M, Fujisaki J. Efficacy of novel sedation using the combination of dexmedetomidine and midazolam during endoscopic submucosal dissection for esophageal squamous cell carcinoma. Esophagus. 2019: 285 [PMID: 30937573 https://doi.org/10.1007/s10388-019-00666-z]

18. Lee SP, Sung IK, Kim JH, Lee SY, Park HS, Shim CS, Hwang HK, Kim TY, Shim SG. Comparison of dexmedetomidine with on-demand midazolam versus midazolam alone for procedural sedation during endoscopic submucosal dissection of gastric tumor. J Dig Dis. 2015: 377 [PMID: 25944073 https://doi.org/10.1111/1751-2980.12254]

19. Nonaka T, Inamori M, Miyashita T, Harada S, Inoh Y, Kanoshima K, Matsuura M, Higurashi T, Ohkubo H, Iida H, Endo H, Kusakabe A, Maeda S, Gotoh T, Nakajima A. Feasibility of deep sedation with a combination of propofol and dexmedetomidine hydrochloride for esophageal endoscopic submucosal dissection. Dig Endosc. 2016: 145 [PMID: 26476104 https://doi.org/10.1111/den.12559]

20. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY, Group MACS. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. Anesth Analg. 2010: 47 [PMID: 19713256 https://doi.org/10.1213/ane.0b013e3181ae0856]

21. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG, Group SS. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009: 489 [PMID: 19188334 https://doi.org/10.1001/jama.2009.56]

22. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology. 1992: 1134 [PMID: 1361311 https://doi.org/10.1097/00000542-199212000-00014]

23. Kim HJ, Ahn E. Risk factors for dexmedetomidine-associated bradycardia during spinal anesthesia: A retrospective study. Medicine (Baltimore). 2022: e31306 [PMID: 36316937 https://doi.org/10.1097/MD.0000000000031306]

24. Ashikari K, Nonaka T, Higurashi T, Takatsu T, Yoshihara T, Misawa N, Arimoto J, Kanoshima K, Matsuura T, Fuyuki A, Ohkubo H, Chiba H, Nakajima A. Efficacy of sedation with dexmedetomidine plus propofol during esophageal endoscopic submucosal dissection. J Gastroenterol Hepatol. 2021: 1920 [PMID: 33506496 https://doi.org/10.1111/jgh.15417]

25. Mason KP, Robinson F, Fontaine P, Prescilla R. Dexmedetomidine offers an option for safe and effective sedation for nuclear medicine imaging in children. Radiology. 2013: 911 [PMID: 23449958 https://doi.org/10.1148/radiol.13121232]

26. Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L, Benham T. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. J Burn Care Res. 2009: 599 [PMID: 19506498 https://doi.org/10.1097/BCR.0b013e3181abff90]

27. Iwagami H, Akamatsu T, Matsuyama K, Hanawa Y, Tonomura K, Chikugo E, Ogino S, Morimura H, Shimoyama M, Terashita T, Nakano S, Wakita M, Edagawa T, Konishi T, Matsumoto H, Nakatani Y, Urai S, Seta T, Uenoyama Y, Yamashita Y. Dexmedetomidine is safe and effective for reducing intraprocedural pain in colorectal endoscopic submucosal dissection. DEN Open. 2023: e223 [PMID: 36992692 https://doi.org/10.1002/deo2.223]

28. Kinugasa H, Higashi R, Miyahara K, Moritou Y, Hirao K, Ogawa T, Kunihiro M, Nakagawa M. Dexmedetomidine for conscious sedation with colorectal endoscopic submucosal dissection: a prospective double-blind randomized controlled study. Clinical and Translational Gastroenterology. 2018: https://doi.org/10.1038/s41424-018-0032-5]

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Original Article

Mycophenolate Mofetil for the Treatment of Resistant Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

*Natalie Balassiano[1], Jasmine Tidwell[2], Omar Abdelhalim[1], Mohammed Abusuliman[3], Mahmoud Nassar[4], Azizullah Beran[5], Ivan Cancarevic[6], Hazem Abosheaishaa[1]**

1- Department of Internal Medicine, Icahn School of Medicine at Mount Sinai / NYC Health + Hospitals Queens, New York, NY, USA.
2- Department of Internal Medicine, University of Connecticut, Farmington, CT, USA.
3- Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.
4- Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA.
5-. Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, IN, USA.
6- Department of Medicine, Brigham and Women's Hospital and Massachusetts General Hospital, Boston, MA, USA.

ARTICLE INFO

Article history:
Received 19 Dec. 2024
Received in revised form 30 Dec. 2024
Accepted 22 Jan. 2025

Keywords:
Mycophenolate Mofetil
Inflammatory Bowel Disease
Crohn's Disease
Ulcerative Colitis
Systematic Review
Meta-Analysis

ABSTRACT

Background: This systematic review evaluates the efficacy and safety of Mycophenolate Mofetil (MMF) for managing treatment-resistant Inflammatory Bowel Disease (IBD), emphasizing remission rates and adverse effects.
Methods: Observational and controlled trials assessing MMF's impact on IBD were included, excluding non-English and pediatric studies. Comprehensive searches were conducted in Embase, Medline/PubMed, Scopus, and Web of Science through October 2023. The risk of bias was evaluated using the NIH quality assessment tool, and results were synthesized using a random-effects meta-analysis model.
Results: Twelve studies comprising 446 participants (333 with Crohn's disease and 113 with ulcerative colitis) were analyzed. The meta-analysis revealed remission rates of 62.2% at 8 weeks and 52.8% at 6 months. Adverse effects occurred in 26.1% of patients, with nausea and vomiting being the most common. Treatment discontinuation due to failure and intolerance was observed in 29.7% and 20% of cases, respectively.
Discussion: The findings suggest that MMF effectively induces remission in IBD patients unresponsive to conventional therapies, although a notable proportion experienced adverse events or treatment failure. Careful patient selection and monitoring are essential.
Conclusion: MMF presents a promising alternative for managing resistant IBD, but its adverse effect profile warrants cautious application. Further research is needed to optimize dosing strategies and assess long-term outcomes in this challenging patient population. These results underscore the potential of MMF as an effective therapeutic option while emphasizing the importance of individualized treatment plans and rigorous clinical monitoring. Future studies should focus on long-term safety and dosing. Additional robust research is required.

1. Introduction:

Inflammatory bowel disease (IBD) is categorized into two subtypes: Crohn's disease (CD) and ulcerative colitis (UC). The causes of IBD are unknown, however, the mechanism involves hyperactive immune-mediated inflammation. Some studies have shown a genetic aspect associated with the genetic influence on the composition of the microbiome as well as common susceptible gene loci found in IBD patients influencing its pathogenesis [1]. IBD is suspected through clinical symptoms and lab findings, however, the gold standard for the diagnosis is endoscopy/colonoscopy with a biopsy of the affected area showing specific histological features [2] In Crohn's disease, the inflammation extends through all layers of the intestinal tissue and can affect any part of the intestinal tract, from mouth to anus. "Skipped lesions" are often seen, which is important when obtaining a tissue biopsy and determining the extent of the disease. In UC, inflammation is

* ***Corresponding author:*** *Hazem Abosheaishaa, Internal Medicine Department, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals Queens, NY, USA. Email Address: hazemabosheaishaa@gmail.com.*

ISSN (Print): 3066-4004, ISSN (Online): 3066-4012 – See front matter

Citation: Balassiano N, Tidwell J, Abdelhalim O, et al. Mycophenolate Mofetil for the Treatment of Resistant Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. ASIDE GI. 2025;1(1):15-22. doi:10.71079/ASIDE.GI.03132515

https://doi.org/10.71079/ASIDE.GI.03132515
Journal homepage: https://asidejournals.com/index.php/Gastroenterology

limited to the mucosal layer of the colon; commonly originating in the rectum and extending up to involve the entire colon continuously [3]. Complications unique to severe CD involve fistula formation, abscess formation, and strictures. A major complication unique to UC is toxic megacolon, which if not treated immediately, can result in colon rupture and can lead to sepsis and death [4]. Inflammatory bowel disease (IBD) is widely accepted as one of the important risk factors leading to colorectal cancer (CRC). Patients with IBD are at a significantly increased risk of CRC, primarily due to the pro-neoplastic effects of chronic intestinal inflammation. The risk of CRC in IBD is influenced by factors such as disease duration, extent, and severity, the presence of inflammatory pseudopolyps, coexistent primary sclerosing cholangitis, and a family history of CRC [5].

Mycophenolate Mofetil (MMF) is a 2-morpholinoethyl ester, a prodrug that gets converted to mycophenolic acid (MPA). MPA is a non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase, an enzyme involved in the purine biosynthesis pathway. Its effect on the de novo synthesis of purines allows it to play a role as an immunosuppressant [6]. In earlier years, MMF was only FDA-approved for use for prophylaxis of organ transplant rejection. Given its mechanism of action, MMF has since been used for the treatment of a plethora of inflammatory/autoimmune conditions. Its first “off-label” use was for psoriasis. [7]. Many trials have then been done showing its efficacy and tolerability, and therefore it has become well-suited as a monotherapy or in combination with corticosteroids. MMF is also found to be effective in patients unresponsive or contraindicated to other immunomodulating agents as well as in cases of steroid-sparing treatment. Overall, MMF is very well tolerated with the most common side effects being gastrointestinal, diarrhea, nausea, and vomiting [8]. With the many variations in the presentation of Inflammatory bowel disease, as well as the variation in medication response and side effects, it's important to consider all the possibilities to present to patients as a treatment plan. Mycophenolate mofetil is one immunomodulator that isn't commonly used, however, given its mechanism of action, it may be a good option for certain individuals suffering from IBD. In this systematic review and meta-analysis, we aimed to study the efficacy and safety of MMF in the management of resistant IBD, focusing on remission rates at eight weeks and six months which is defined as the absence or significant reduction of symptoms associated with the disease.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [9, 10].

2.1. Search strategy:

A broad search was done using the following databases: Embase, Medline/ PubMed, Scopus, and Web of Science. The search was conducted using Boolean search strategies and the following keywords from the MeSH database were used: (“Ulcerative colitis” OR “Crohn's disease” OR “Crohn’s disease” OR “UC” OR “CD” OR “IBD” OR “Inflammatory bowel disease” OR “Colitis, Ulcerative” OR "Crohn Disease" OR "Inflammatory Bowel Diseases") AND (“Mycophenolate” OR “mycophenolate mofetil” OR “MMF” OR “Mycophenolic acid” OR “Sodium mycophenolate” OR “Cellcept” OR "Mycophenolic Acid"). A preliminary database search was done from inception till October 2023. Two independent co-authors utilized the Covidence website to perform screening and remove duplicate studies, with a third reviewer resolving any disagreements.

2.2. Eligibility criteria:

Articles included were prospective and retrospective observational case-control, cohort studies as well as randomized controlled clinical trials. Articles excluded were narrative reviews, systematic reviews, case reports, abstracts, and case studies conducted on animals and pediatrics. Letters and articles in languages other than English as well as studies that did not meet the required National Institute of Health (NIH) quality assessment score.

2.3. Data extraction:

Data was extracted into an Excel sheet by two co-authors and validated with a third co-author.

2.4. Outcomes:

The outcomes of this study are defined as follows: First, remission rates at eight weeks and six months are assessed, where remission is identified as either the absence or a significant reduction of symptoms commonly associated with the disease. These symptoms include abdominal pain, diarrhea, rectal bleeding, fatigue, and weight loss. Secondly, steroid-free remission is measured, characterized by a marked clinical improvement—specifically, a reduction of three or more points on the Harvey-Bradshaw Index for Crohn's disease and two or more points on the Mayo Partial Score for UC from baseline. This improvement must also coincide with a decrease in steroid dosage or a complete cessation. Finally, the study examines the overall incidence of adverse effects to evaluate the safety profile of the treatment and its potential as an alternative therapeutic option. These defined outcomes aim to provide a comprehensive understanding of the treatment's efficacy and safety.

2.5. Quality assessment:

Quality appraisal was performed by two co-authors using the NIH quality assessment tool and articles scoring no less than three points below the maximum score for the type of article were included in the final review.

2.6. Statistical analysis:

Pooled proportions of event rates and corresponding 95% confidence intervals (CIs) were calculated using a proportion meta-analysis with the random-effects model for remission rate (at eight weeks, six months, and steroid-free remission) and safety outcomes including discontinuation rate due to treatment failure or medication intolerance and overall adverse events (including nausea/vomiting, diarrhea, infections, and deranged liver function) for individuals subjected to MMF for IBD. A random effects model was applied to accommodate variations in study sizes. Heterogeneity was evaluated using I2 statistics, where values falling within <30%, 30% to 60%, 61% to 75%, and >75% were categorized as low, moderate, substantial, and considerable heterogeneity, respectively. Between-study sources of heterogeneity were examined through predefined subgroup analyses, and a P value for differences between subgroups of < .05 was considered statistically significant. Comprehensive Meta-Analysis software (version 2, Biostat, Englewood, NJ) was utilized for all analyses.

3. Results:

3.1: Search results and patient characteristics:

The initial search retrieved 3184 studies, 2622 of them underwent title and abstract screening, and 147 full texts were assessed for inclusion. A total of twelve studies were found to be eligible and have been pooled in this meta-analysis. The total number of IBD patients included in the study was 446 patients. 333 (74.6%) patients had CD, 107 (23.9%) patients had UC, 5 (1.1%) patients had UC/unspecified colitis, and 1 patient had unspecified colitis. The average age of participants was 38.4 years (range 25-42) and males made up 38.7% of the studied population. The mean duration of MMF therapy was 11.4 months. The rest of the baseline characteristics and summaries of the studies are demonstrated in (Table 1).

3.2. Meta-analysis results:

3.2.1. Remission at 8 weeks:

The forest plot illustrates rates of remission at eight weeks and 95% CI. The area of the black square is proportional to the specific study weight of the overall meta-analysis. The center of the red diamond displays the pool of overall rate of remission at eight weeks, and its width shows the pooled 95% CI. Five studies were pooled with an overall rate of 62.2% with a 95% CI from 0.426 to 0.785 (figure 2).

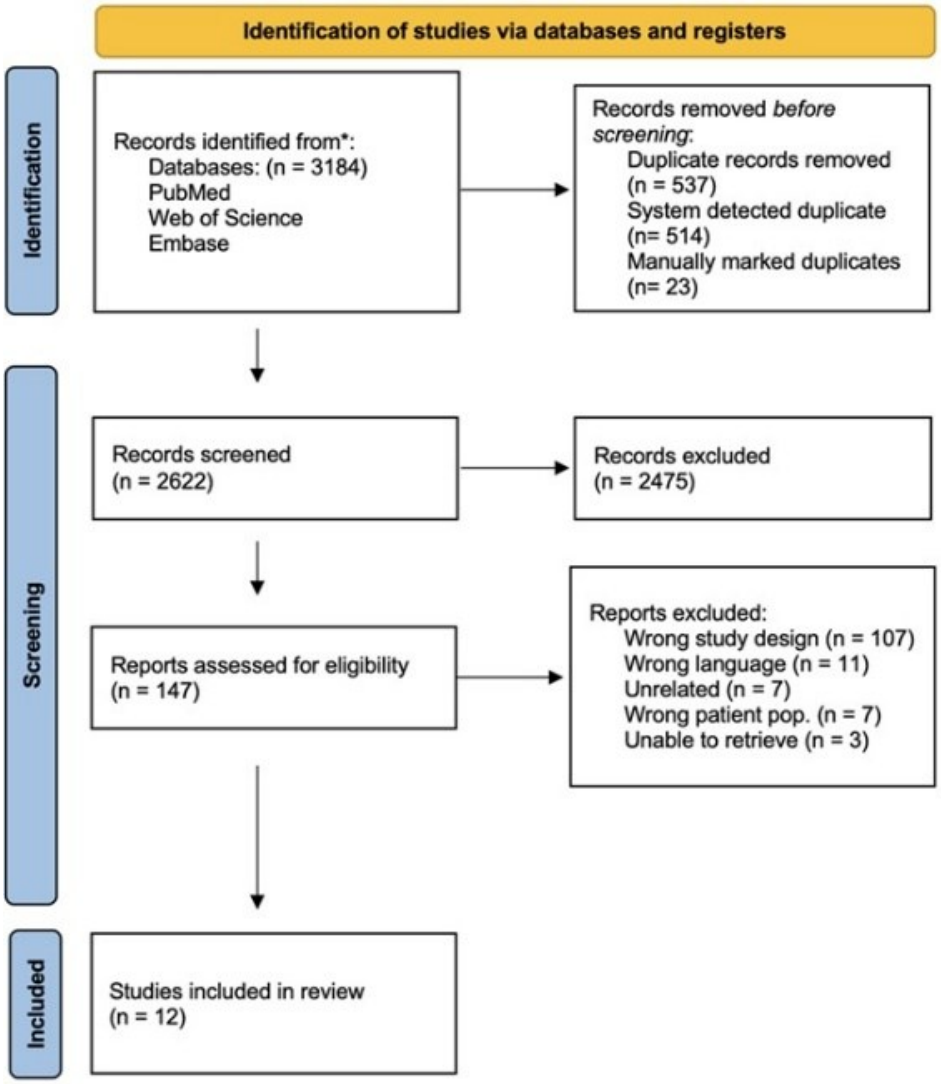

Figure 1: Show the PRISMA flow diagram of our search.

3.2.2. Remission at 6 months:

Regarding six-month remission rates, seven studies were pooled with an overall rate of 52.8% with a 95% CI from 0.366 to 0.684 (figure 3).

3.2.3. Steroid-free remissions:

For steroid-free remission, 4 studies were pooled. The pooled steroid-free remission rate was 53.3% with a 95% CI from 0.246 to 0.80 (figure 4).

3.2.4. Overall Incidence of Adverse Effects:

Twelve studies have been pooled in this analysis. The rate of total incidence of side effects pooled from this analysis is (26.1%) with a 95% CI from 0.203 to 0.328 (figure 5).

Subgroup analysis was done reporting different side effects: Nausea and Vomiting were the most frequently reported side effects where data from eight studies were pooled with an overall rate of 21.2% (8.5%-43.9%), 95% CI. The pooled rate of arthralgia incidence was 15.5% (7.9%-27.9%) with 95% CI. The pooled rate of diarrhea incidence was 13.6% (7.6%-23%) with 95% CI. The pooled incidence of skin rash was 12.6% (5.2%-27.5%) with 95% CI. The pooled rate of infection incidence was 12.6% (5%-28%) with 95% CI. The pooled incidence of deranged liver function was 7.5% (2.8%-18.7) with 95% CI. (Supplementary table).

3.2.5. Discontinuation rate due to failure:

Failure to induce remission was the most common cause of drug discontinuation. The pooled rate was 29.7% with a 95% CI from 0.175 to 0.457 (figure 6).

3.2.6. Discontinuation due to intolerance:

The pooled rate of drug discontinuation due to intolerance was 20% with a 95% CI from 0.123 to 0.309 (figure 7).

4. Discussion

Our study encompassed a systematic search that ultimately yielded twelve eligible studies involving 446 patients with IBD, predominantly with Crohn's disease (74.6%) and ulcerative colitis (23.9%). Patient demographics revealed an average age of 38.4 years, with males comprising 38.7% of the cohort. The meta-analysis unveiled promising outcomes: remission rates at 8 weeks (62.2%), 6 months (52.8%), and steroid-free remission (53.3%). Additionally, the pooled incidence of side effects was 26.1%, with nausea/vomiting being the most prevalent (21.2%). Discontinuation rates due to failure (29.7%) and intolerance (20%) were notable, underscoring the importance of adverse event management and treatment efficacy in IBD therapy.

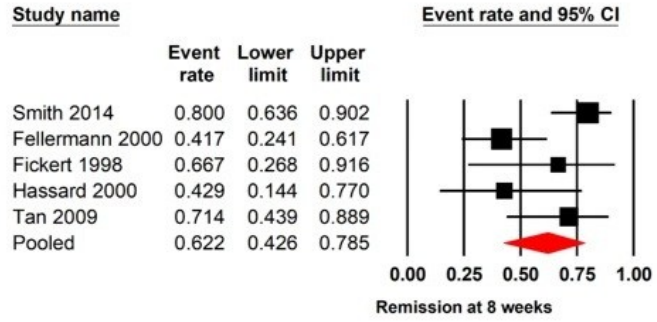

Figure 2: Forest plot illustrates the rate of remission at 8 weeks.

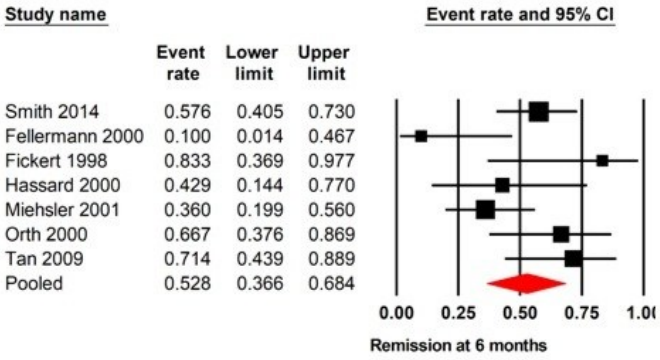

Figure 3: Forest plot illustrates the rate of remission at 6 months.

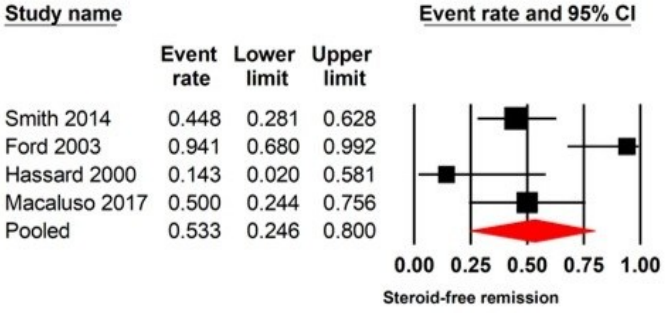

Figure 4: Forest plot illustrates the rate of steroid free remission.

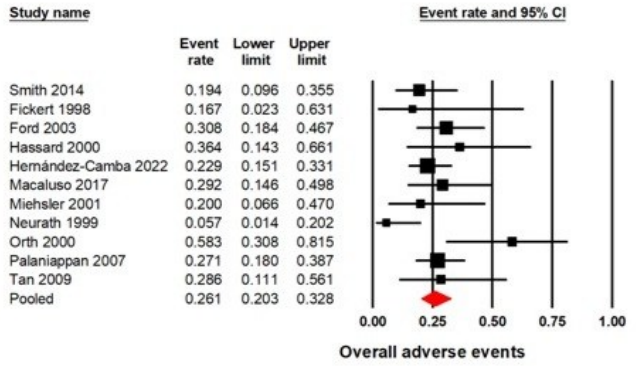

Figure 5: Forest plot illustrates the rate of total adverse events.

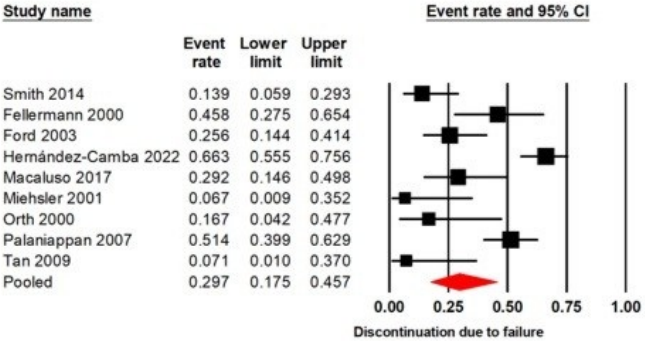

Figure 6: Forest plot illustrates the rate of discontinuation due to failure.

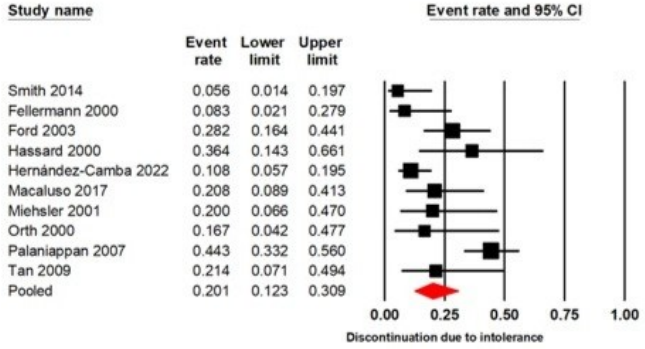

Figure 7: Forest plot illustrates the rate of discontinuation due to intolerance.

As we continue to learn the multifactorial risk factors contributing to IBD, we must also investigate the right medications to manage this disease. Since each patient is unique in their presentation of IBD, their medication responsiveness is just as unique. To better explore and understand the effectiveness and indications of Mycophenolate Mofetil in the treatment of inflammatory bowel disease, we included 12 high-quality articles. In these articles, there appears to be an effective treatment therapy with the use of MFF for IBD.

Aminosalicylates (5-ASA), whether administered orally or topically, are efficacious in both initiating and sustaining remission in cases of moderate UC. These medications sometimes give rise to adverse symptoms such as nausea, fever, and rash. Glucocorticoids are the preferred first treatment for moderate to severe UC to induce remission. However, they are not recommended for long-term maintenance due to their major adverse effects on several organs, such as Cushing's syndrome (e.g., insulin resistance, high blood pressure, cataracts, avascular necrosis). The process of gradually reducing their dosage should be implemented while simultaneously introducing maintenance treatment [11, 12].

Immunomodulators, such as azathioprine (AZA) and its byproduct mercaptopurine, are glucocorticoid-sparing agents that may be introduced. The most common side effect is leukopenia and therefore all patients are required to have routine blood work. Biologics, including anti-TNF agents and monoclonal antibodies, have been proven to induce and maintain remission in moderate to severe UC. Risk factors of these agents include reactivation of latent infections such as TB and hepatitis B and therefore all patients must be worked up and treated for these infections before starting medication. Lastly, hospitalized patients can be started on cyclosporin, a calcineurin-inhibiting agent, when nonresponsive to IV glucocorticoids with the most common side effects including hyperuricemia, hypertension, and gingival hyperplasia [13]. Treatment for CD varies from that of UC because of its intestinal tract involvement 5-ASA was only shown to be effective in mild CD with colon involvement. Glucocorticoids are effective in inducing remission in moderate to severe CD, however just like in UC, should not be used for maintenance therapy. Immunomodulators are also effective in CD as a glucocorticoid-sparing treatment however have not been shown to induce remission. Methotrexate was found to be effective in maintaining

Author and year	Study Type	Country	No. of Pt	UC	CD	Main Inclusion Criteria	Intervention	Previous TTT
Smith 2014 [22]	Retrospective	UK	36	12	19	All patients who had received MMF for IBD.	500 mg and 2 g daily (median dose 1 g), titrated to a dose of 2 g daily were tolerated.	9 Corticosteroid 33 AZA 7 6-MP 2 MTX 3 infliximab
Neurath 1999 [23]	RCT	Germany	70	NA	70	patients with chronic active CD for at least one year and had a minimum of three acute flares within the previous three years.	15 mg/kg MMF plus 50 mg Vs 2.5 mg/kg AZA plus 50 mg prednisolone orally.	NA
Hassard 2000 [15]	CT	USA	11	NA	11	CD patients who required immunomodulator therapy and had failed or been intolerant to conventional immunomodulators therapy with 6-MP/AZA or MTX.	1-3 g of MMF in two divided doses.	8 Corticosteroid 11 AZA 3 MTX 3Cyclosporin
Palaniappan 2007 [24]	Retrospective	UK	70	19	51	CD patients received MMF specifically for inflammatory bowel disease over 5 years (2000–2005).	1.5 g MMF daily (range, 1–2 g daily).	67 Azathioprine 7 MTX 5 Cyclosporin 4 Infliximab
Fellermann 2000 [19]	Prospective uncontrolled trial	Germany	24	13	11	continuing active disease over the last 2 months, despite a daily steroid dose of 10 mg or more of prednisone-equivalent (range 10±60 mg, median 20 mg prednisone equivalent).	A steroid dose of 60 mg of prednisone was given orally together with MMF 1 g/day. then MMF 1.5 g/day after 1 wk then 2 g/day after 2 wks /Prednisone was tapered in 5 mg per wk. followed by a maintenance dose of 5 mg/day after 12 wks.	NA
Ford 2003 [16]	Retrospective	UK	39	7	32	patients who had received MMF mofetil specifically for the treatment of IBD.	MMF 1.5 g/day (range 1–2 g/day).	38 Corticosteroid 37 AZA 3 6-MP 5 MTX 3 Cyclosporin 5 Infliximab
Fickert 1998 [17]	CT	Austria	6	NA	6	patients with CD who did not tolerate azathioprine.	2 g/day of mycophenolate	5 Corticosteroid 3 AZA
Macaluso 2017 [25]	Prospective	Italy	24	11	13	All consecutive patients with moderate-to-severe CD or UC and previous multiple failure and/or intolerance to IM and biologics.	1000 mg daily for 15 days in all patients and then titrated to a median dose of maintenance of 1500 mg/day (range: 1000–2000 mg/day).	NA
Miehsler 2001 [18]	Retrospective	Austria	45	NA	45	chronic active CD in whom therapy with MMF had been initiated after intolerance to AZA.	MMF 25–35 mg/kg.	15 Azathioprine Corticosteroid
Hernández-Camba 2022 [26]	Retrospective	Spain	83	17	66	IBD patients aged ≥18 years who had ever received MMF were identified.	MMF 1269.8 ± 741 mg/day.	NA
Orth 2000 [27]	RCT	Germany	24	24	NA	at least 18 years old and had a confirmed diagnosis of active UC according to standard clinical and endoscopic criteria, with a minimum of three acute relapses since diagnosis.	MMF (20mg/kg) / prednisolone Vs AZA (2 mg/kg) prednisolone.	NA
Tan 2009 [28]	CT	Australia	14	5	9	CD or ulcerative colitis/IBD unclassified.	MMF 500 mg and 2000 mg twice a day.	10 Corticosteroid 13 AZA 13 6-MP 7 MTX 8 Infliximab

Pt: Patient; TTT: treatment; UC: Ulcerative Colitis; CD: Crohn's Disease; MMF: Mycophenolate Mofetil; AZA: Azathioprine; 6-MP: 6-Mercaptopurine; MTX: Methotrexate; IBD: Inflammatory bowel disease: IBD; RCT: Randomized Controlled Trial; CT: Clinical Trial; NA: Not Available.

Table 1: Summary of Clinical Research on Mycophenolate Mofetil (MMF) for the Management of Crohn's Disease and Ulcerative Colitis

remission and alleviating corticosteroid dependency, however, it puts patients at risk of interstitial pneumonitis and can cause hepatotoxicity. Biologics are recommended for moderate to severe CD, mostly effective as a combination therapy versus monotherapy [13].

Overall, our analysis studies have shown that MMF has been used particularly in patients who are steroid-dependent and are refractory or intolerant to more conventional therapies. A significant portion of patients are refractory to conventional therapies, making alternative management a hot topic. Studies were primarily conducted on IBD patients unresponsive, intolerant, or contraindicated for azathioprine. Patients often discontinue the drug due to unresponsiveness resulting in disease relapse, or the event of undesired adverse effects such as pancreatitis, infections, and hepatitis. In a cross-sectional study by Lee et al., they discuss the intolerance of AZA as a predictor of a poor prognosis, indicating patients with a more aggressive disease course [14]. Hassard et al. correlated resistance to AZA as a predictor of resistance to MMF, and resistance to AZA categorized patients as having severe IBD. Those unresponsive to AZA and MFF perhaps have an IBD that is resistant to the effects of purine synthesis inhibitors [15]. Some studies have shown that patients have a deficiency in thiopurine methyltransferase (TPMT), the enzyme that metabolizes azathioprine. With the reduction in the drugs' metabolism, patients are at an increased risk of bone marrow suppression, making AZA a poor option. [16]. The most undesirable reported adverse event with AZA, is AZA-induced pancreatitis. In Fickert et al., 40% of the patients entered in the study after AZA-induced pancreatitis. Another patient was unable to start AZA because of prior mesalamine severe drug-induced pancreatitis, making AZA a poor option for them [17]. Miehsler et al, compared two study groups and reported pancreatitis in 13% of patients, with another 10% showing elevated lipase in the group on AZA therapy. AZA-induced leukopenia occurred in 13% of the patients' studies in Miehsler et al. whereas no patients on MMF were shown to have leukopenia. Additionally, Miehsler et al. reported the development of monoclonal gammopathy as a result of AZA. Not all side effects resolution was discussed, however, Fickert et al. report all adverse reactions induced by AZA in the patient's studies, had disappeared after the discontinuation of the drug [17, 18].

Our results pooled from this meta-analysis concluded that remission rates vary across periods. The overall remission rate was 62.2% at 8 weeks (95% CI: 42.6%-78.5%); it was marginally lower at 52.8% at 6 months (95% CI: 36.6%-68.4%). The pooled rate for steroid-free remission was 53.3% (95% CI: 24.6%-80%). The results of this study emphasize the significance of taking into account the duration and course of treatment when evaluating remission rates in individuals diagnosed with UC. Ford et al. report successful control of IBD with MMF in 41% of the studied patients with an average of 18 months of therapy. All of these patients were on steroids at the time of initiating MMF, however were no longer on steroids at the time of review. This allows us to consider MMF as a bridge therapy to remission in refractory patients. Miehsler et al. reported a significant reduction in the cumulative intake of prednisone within the first 6 months of MMF use, compared to no reduction in the prednisone intake in those on AZA. This alone can help guide treatment options as chronic steroid use is associated with very SEVER long-term side effects. If tapering and cessation of steroids can be achieved quicker with MMF, it may be more favorable to avoid long-term risks associated with prolonged steroid use. This earlier onset of the therapeutic effect of MMF is also seen in transplant survival studies comparing MMF and AZA and the reduction of rejection episodes [18].

In a study done by Hernandez-Camba et al., clinical efficacy was seen in 71% of patients in whom MMF was added to their biologic regimen. This concomitant use of combined therapy can allow clinicians to consider adding MMF to a patient's developing secondary non-response to anti-TNF alpha monotherapy. Furthermore, Fellermann et al. involved patients who were started on combined therapy of prednisone and MMF in the first block, followed by a decrease in prednisone and an increase in MMF in the second block. This helps us see the effects of dual therapy of prednisone for induction of remission along with MMF as a bridge to monotherapy with just MMF. The study, however, reported decreased success as the steroids were tapered, indicating perhaps too early taper. Following this, those patients received a steroid pulse, and eventually about 42% of patients reached remission and maintained remission after the steroid taper [19]. This may reflect the delayed onset of drug onset, leading us to consider the length of therapy required to reach drug efficacy.

When introducing a drug for medical management, it is important to understand the possibility and likelihood of adverse events. Our analysis of overall adverse effects in twelve pooled studies reveals an incidence rate of 26.1% (95% CI: 20.3%-32.8%). Subgroup analysis further delineates specific adverse events, with nausea and vomiting being the most frequently reported side effects, with an overall rate of 21.2% (95% CI: 8.5%-43.9%). Arthralgia follows, with a pooled rate of 15.5% (95% CI: 7.9%-27.9%), while diarrhea and skin rash show rates of 13.6% (95% CI: 7.6%-23%) and 12.6% (95% CI: 5.2%-27.5%), respectively. Additionally, the incidence of infection and deranged liver function were reported at 12.6% (95% CI: 5%-28%) and 7.5% (95% CI: 2.8%-18.7%), respectively. These findings underscore the need for careful monitoring and management of adverse effects in UC treatment to optimize patient care and outcomes. In addition to the specific adverse effects reported, the rate of medication discontinuation due to intolerance is a critical aspect of treatment evaluation. The pooled rate of drug discontinuation attributable to intolerance was found to be 20% (95% CI: 12.3%-30.9%) in the context of the aforementioned adverse events. This highlights the significant impact of side effects on treatment adherence and underscores the importance of balancing efficacy with tolerability in UC management strategies. Efforts to minimize adverse events and improve patient tolerability are essential to reduce the likelihood of treatment discontinuation and optimize long-term therapeutic outcomes.

In contrast, thiopurines are associated with specific risks, such as leukopenia, pancreatitis, and hepatotoxicity, while biologics carry risks of infections and immunogenicity leading to loss of response [20, 21]. However, without direct comparative studies, it remains challenging to definitively evaluate MMF's safety profile relative to these therapies.
Clinical implications: Based on the comprehensive analysis of various treatment options and their associated adverse effects, MMF emerges as a promising alternative for patients who cannot tolerate other conventional steroid-sparing agents, such as azathioprine, or other medications for IBD. The study findings demonstrate MMF's efficacy in inducing and maintaining remission, particularly in patients who are steroid-dependent or refractory to other therapies. Notably, MMF shows a favorable adverse effect profile compared to azathioprine, with lower rates of adverse events such as leukopenia and pancreatitis, which are common concerns with azathioprine therapy. Additionally, MMF may offer quicker tapering of steroid use, reducing the risk of long-term steroid-related complications. Furthermore, MMF can be considered in combination with biological agents for patients experiencing secondary non-response, potentially enhancing treatment outcomes. Although MMF is not without its side effects, careful monitoring and management can help mitigate adverse events and optimize therapeutic benefits. Therefore, MMF represents a valuable treatment option for patients with IBD who have failed or cannot tolerate other medications, offering a potential pathway to achieve and maintain remission while minimizing the risk of treatment-related complications.

Limitations: This is a single-arm analysis with a lack of a control group which makes it challenging to establish a causal relationship between the intervention and outcomes. Without a comparator, it's difficult to determine whether observed effects are solely attributable to the intervention or influenced by other factors. Another limitation of this study is its focus on patients with steroid dependence and refractoriness or intolerance to conventional therapies, primarily azathioprine, within the IBD population as those patients do not fully represent the broader spectrum of patients with IBD who may respond differently to treatments or have different underlying conditions.

Recommendation: Existing studies have focused on MMF in refractory or steroid-dependent IBD patients, leaving a gap in evidence for its use in early disease management. To date, randomized controlled trials (RCTs) specifically evaluating MMF as a first-line therapy in newly diagnosed IBD patients are lacking. This absence of robust data limits our understanding of MMF's safety, efficacy, and positioning in the early treatment algorithm for IBD, consequently, new RCTs testing the

efficacy and safety of MMF in newly diagnosed IBP patients are warranted.

5. Conclusion:

In conclusion, our study shed light on the potential of MMF as a treatment option for IBD. Despite limitations, including a lack of a control group, our findings suggest that MMF holds promise, particularly for individuals who are steroid-dependent or refractory to conventional steroid-sparing therapies. MMF demonstrates efficacy in inducing and maintaining remission, with a favorable adverse effect profile compared to some traditional treatments like azathioprine. However, further research, particularly prospective randomized controlled trials comparing MMF to standard treatments, is needed to better understand its role in IBD management.

Conflicts of Interest:

None

Ethical Approval:

None

Funding Source:

None

Acknowledgements:

None

Institutional Review Board (IRB) Approval:

None

LLM Statement:

None

Authors Contribution Statement:

H.A., A.A., A.A., A.S., A.I., D.M., M.A., O.A., I.M., A.Y.A., M.N., and M.B. contributed equally to the conception, study design, data acquisition, statistical analysis, and interpretation of the findings in this research. All authors actively participated in drafting the manuscript and critically revising it for intellectual content. They have provided final approval for the version to be published and affirm their accountability for all aspects of the work, ensuring that any concerns regarding accuracy or integrity are thoroughly investigated and resolved.

Data Availability Statement:

All data generated or analyzed during this study are included in this published article. The data are publicly available and have been cited appropriately within the text of the document.

References

1. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. World J Gastroenterol. 2014: 91 [PMID: 24415861 https://doi.org/10.3748/wjg.v20.i1.91]

2. Moazzami B, Moazzami K, Rezaei N. Early onset inflammatory bowel disease: manifestations, genetics and diagnosis. Turk J Pediatr. 2019: 637 [PMID: 32104994 https://doi.org/10.24953/turkjped.2019.05.001]

3. Rodrigues BL, Mazzaro MC, Nagasako CK, Ayrizono MLS, Fagundes JJ, Leal RF. Assessment of disease activity in inflammatory bowel diseases: Non-invasive biomarkers and endoscopic scores. World J Gastrointest Endosc. 2020: 504 [PMID: 33362904 https://doi.org/10.4253/wjge.v12.i12.504]

4. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. World J Gastroenterol. 2006: 4819 [PMID: 16937463 https://doi.org/10.3748/wjg.v12.i30.4819]

5. Kim ER, Chang DK. Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. World J Gastroenterol. 2014: 9872 [PMID: 25110418 https://doi.org/10.3748/wjg.v20.i29.9872]

6. Chakrabarti K, Frame D, Al Abbas M, McCune WJ. The use of mycophenolate mofetil area under the curve. Curr Opin Rheumatol. 2021: 221 [PMID: 33741807 https://doi.org/10.1097/BOR.0000000000000799]

7. Orvis AK, Wesson SK, Breza TS, Jr., Church AA, Mitchell CL, Watkins SW. Mycophenolate mofetil in dermatology. J Am Acad Dermatol. 2009: 183 [PMID: 19150270 https://doi.org/10.1016/j.jaad.2008.08.049]

8. Surjushe A, Saple DG. Mycophenolate mofetil. Indian J Dermatol Venereol Leprol. 2008: 180 [PMID: 18388396 https://doi.org/10.4103/0378-6323.39725]

9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010: 336 [PMID: 20171303 https://doi.org/10.1016/j.ijsu.2010.02.007]

10. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019: ED000142 [PMID: 31643080 https://doi.org/10.1002/14651858.ED000142]

11. Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020: CD000543 [PMID: 32786164 https://doi.org/10.1002/14651858.CD000543.pub5]

12. Bruscoli S, Febo M, Riccardi C, Migliorati G. Glucocorticoid Therapy in Inflammatory Bowel Disease: Mechanisms and Clinical Practice. Front Immunol. 2021: 691480 [PMID: 34149734 https://doi.org/10.3389/fimmu.2021.691480]

13. Jeong DY, Kim S, Son MJ, Son CY, Kim JY, Kronbichler A, Lee KH, Shin JI. Induction and maintenance treatment of inflammatory bowel disease: A comprehensive review. Autoimmun Rev. 2019: 439 [PMID: 30844556 https://doi.org/10.1016/j.autrev.2019.03.002]

14. Lee LYW, Gardezi AS, Santharam V, Boyd J, Lanzon-Miller S. Effect of azathioprine intolerance on outcomes of inflammatory bowel disease: a cross-sectional study. Frontline Gastroenterol. 2014: 40 [PMID: 28839749 https://doi.org/10.1136/flgastro-2013-100348]

15. Hassard PV, Vasiliauskas EA, Kam LY, Targan SR, Abreu MT. Efficacy of mycophenolate mofetil in patients failing 6-mercaptopurine or azathioprine therapy for Crohn's disease. Inflamm Bowel Dis. 2000: 16 [PMID: 10701145 https://doi.org/10.1097/00054725-200002000-00003]

16. Ford AC, Towler RJ, Moayyedi P, Chalmers DM, Axon AT. Mycophenolate mofetil in refractory inflammatory bowel disease. Aliment Pharmacol Ther. 2003: 1365 [PMID: 12786630 https://doi.org/10.1046/j.1365-2036.2003.01581.x]

17. Fickert P, Hinterleitner TA, Wenzl HH, Aichbichler BW, Petritsch W. Mycophenolate mofetil in patients with Crohn's disease. Am J

Gastroenterol. 1998: 2529 [PMID: 9860419 https://doi.org/10.1111/j.1572-0241.1998.00606.x]

18. Miehsler W, Reinisch W, Moser G, Gangl A, Vogelsang H. Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? Am J Gastroenterol. 2001: 782 [PMID: 11280551 https://doi.org/10.1111/j.1572-0241.2001.03622.x]

19. Fellermann K, Steffen M, Stein J, Raedler A, Hamling J, Ludwig D, Loeschke K, Stange EF. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. Aliment Pharmacol Ther. 2000: 171 [PMID: 10651657 https://doi.org/10.1046/j.1365-2036.2000.00695.x]

20. Lim SZ, Chua EW. Revisiting the Role of Thiopurines in Inflammatory Bowel Disease Through Pharmacogenomics and Use of Novel Methods for Therapeutic Drug Monitoring. Front Pharmacol. 2018: 1107 [PMID: 30349479 https://doi.org/10.3389/fphar.2018.01107]

21. Velikova T, Sekulovski M, Peshevska-Sekulovska M. Immunogenicity and Loss of Effectiveness of Biologic Therapy for Inflammatory Bowel Disease Patients Due to Anti-Drug Antibody Development. Antibodies (Basel). 2024: [PMID: 38534206 https://doi.org/10.3390/antib13010016]

22. Smith MR, Cooper SC. Mycophenolate mofetil therapy in the management of inflammatory bowel disease--a retrospective case series and review. J Crohns Colitis. 2014: 890 [PMID: 24507162 https://doi.org/10.1016/j.crohns.2014.01.014]

23. Neurath MF, Wanitschke R, Peters M, Krummenauer F, Meyer zum Buschenfelde KH, Schlaak JF. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. Gut. 1999: 625 [PMID: 10205197 https://doi.org/10.1136/gut.44.5.625]

24. Palaniappan S, Ford AC, Greer D, Everett SM, Chalmers DM, Axon AT, Hamlin PJ. Mycophenolate mofetil therapy for refractory inflammatory bowel disease. Inflamm Bowel Dis. 2007: 1488 [PMID: 17924566 https://doi.org/10.1002/ibd.20258]

25. Macaluso FS, Maida M, Renna S, Orlando E, Affronti M, Sapienza C, Dimarco M, Orlando R, Rizzuto G, Cottone M, Orlando A. Mycophenolate mofetil is a valid option in patients with inflammatory bowel disease resistant to TNF-alpha inhibitors and conventional immunosuppressants. Dig Liver Dis. 2017: 157 [PMID: 27876682 https://doi.org/10.1016/j.dld.2016.10.001]

26. Hernandez-Camba A, Arranz L, Vera I, Carpio D, Calafat M, Lucendo AJ, Taxonera C, Marin S, Garcia MJ, Marin GS, Rodriguez ES, Carbajo AY, De Castro ML, Iborra M, Martin-Cardona A, Rodriguez-Lago I, Busquets D, Bertoletti F, Ausin MS, Tardillo C, Malaves JH, Bujanda L, Castano A, Domenech E, Ramos L, Geteccu, Additional member of the Spanish Gg. Real-world use of mycophenolate mofetil in inflammatory bowel disease: Results from the ENEIDA registry. Dig Liver Dis. 2022: 635 [PMID: 34862115 https://doi.org/10.1016/j.dld.2021.10.002]

27. Orth T, Peters M, Schlaak JF, Krummenauer F, Wanitschke R, Mayet WJ, Galle PR, Neurath MF. Mycophenolate mofetil versus azathioprine in patients with chronic active ulcerative colitis: a 12-month pilot study. Am J Gastroenterol. 2000: 1201 [PMID: 10811328 https://doi.org/10.1111/j.1572-0241.2000.02010.x]

28. Tan T, Lawrance IC. Use of mycophenolate mofetil in inflammatory bowel disease. World J Gastroenterol. 2009: 1594 [PMID: 19340901 https://doi.org/10.3748/wjg.15.1594]

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Original Article

Insights into the Epidemiology and Determinants of Helicobacter Pylori Negative Gastritis: A Retrospective Study

Ahmed E. Salem[1], Syed Matthew Kodilinye[1], Morad Zaaya[1], Carla Barberan Parraga[1], Sarah Meribout[1], Samar Pal S. Sandhu[1], Cherry Aye[1], Kantash Kumar[1], Joseph A. Menand[2], Neha Sharma[2], MariaLisa Itzoe[2], Tanuj R. Chokshi[2], Mohammed Abusuliman[3], Islam Mohamed[4], Hazem Abosheaishaa[5], Yuriy Tsirlin[2]*

1- Internal Medicine Department, Maimonides Medical Center, Brooklyn, New York, NY, USA.
2- Gastroenterology Department, Maimonides Medical Center, Brooklyn, New York, NY, USA.
3- Internal Medicine Department, Henry Ford Hospital, Detroit, MI, USA.
4- Gastroenterology Department, University of Missouri-Kansas City, Mo, USA.
5- Internal Medicine Department, Icahn School of Medicine at Mount Sinai / NYC Health + Hospitals Queens, New York, NY, USA.

ARTICLE INFO

Article history:
Received 14 Nov. 2024
Received in revised form 17 Dec. 2024
Accepted 22 Dec. 2024

Keywords:
Antral biopsies
Chronic gastritis
Chronic chemical gastritis
Helicobacter pylori
Helicobacter pylori-negative gastritis
Gastroesophageal reflux disease (GERD)

ABSTRACT

Introduction: The prevalence of Helicobacter pylori (HP)-negative gastritis is rising in the United States, yet its origins and risk factors remain largely unexplored. This study aims to assess the prevalence of HP-negative gastritis and explore the demographic, clinical, and risk factor profiles that differentiate HP-negative from HP-positive subjects with histological evidence of gastritis.

Methods: We conducted a retrospective analysis of 241 patients who underwent Esophagogastroduodenoscopy (EGD) for upper gastrointestinal symptoms at a tertiary care center between July 2020 and July 2021. Symptoms prompting referral included dysphagia, abdominal pain, nausea, and others. Gastric biopsies were collected from the antrum and body, and clinical, demographic, and laboratory data were analyzed to compare HP-negative and HP-positive gastritis cases.

Results: Of the patients biopsied, 38.2% (n=92) showed histological evidence of gastritis, with 78% of these being HP-negative and 22% HP-positive. HP-negative cases were predominantly chronic chemical gastritis (61.5%), while all HP-positive cases were active chronic gastritis. Significant ethnic disparities were noted; 61.5% of HP-negative patients were Caucasian, and 72.7% of HP-positive patients were African American. Medical comorbidities, particularly gastroesophageal reflux disease (GERD), were more associated with HP-negative gastritis. The antrum was more frequently affected in HP-negative cases compared to HP-positive cases.

Conclusion: HP-negative gastritis is significantly linked with Caucasian ethnicity and existing medical comorbidities but shows no strong associations with the analyzed lifestyle or medication factors. These findings highlight the need for further large-scale prospective studies to better understand the etiology, risk factors, and clinical implications of HP-negative gastritis.

1. Introduction:

Gastritis is an inflammatory condition of the stomach lining with diverse clinical presentations. Histologically, acute gastritis is identified by the presence of neutrophils whereas chronic gastritis is identified by the presence of lymphocytes and plasma cells. No universally accepted classification of gastritis exists. The Sydney system classifies gastritis based on etiology, topographical distribution of inflammation, and morphological features observed on histologic examination [1]. Helicobacter pylori (*H. pylori*) has long been identified as the leading cause of gastritis and peptic ulcer disease[2]. The Kyoto classification

* ***Corresponding author:*** *Ahmed E. Salem, Internal Medicine Department, Maimonides Medical Center, Brooklyn, New York, NY, USA. Email Address: Ahmed.e.salem@hotmail.com.*

ISSN (Print): 3066-4004, ISSN (Online): 3066-4012 – See front matter

Citation: E. Salem A, Kodilinye SM, Zaaya M, et al. Insights into the Epidemiology and Determinants of Helicobacter Pylori Negative Gastritis: A Retrospective Study. ASIDE GI. 2025;1(1):23-26. doi:10.71079/ASIDE.GI.0315258

https://doi.org/10.71079/ASIDE.GI.0315258
Journal homepage: https://asidejournals.com/index.php/Gastroenterology

uses a scoring system based on the endoscopic findings to assess the presence or absence of *H. pylori* infection and the risk of gastric cancer [3].

Recent studies suggest a decline in the incidence of gastritis which can be attributed to the decreasing prevalence of *H. pylori* in much of the developed world [4-6]. In this evolving epidemiological landscape, a unique entity named *Helicobacter pylori*-negative (HP-negative) gastritis has come to light [7]. This entity was previously assumed to be merely cases of missed *H. pylori* infection. It has been argued that previous use of PPIs [8, 9], and antibiotics[10] may contribute to the eradication or migration of *H. pylori* from the biopsied antrum where they normally colonize, to the corpus, while gastric inflammation persists. Sampling errors have also been implicated in false negative errors in identifying *H. pylori[11]*. Studies using tests with higher sensitivity have been successful in identifying *H. pylori* signals in a small proportion of previously negative samples but a significant portion of these HP-negative cases remain unexplained [12].

The association between *H. pylori* infection and non-cardia gastric cancer is well known [12, 13]. It is unclear as to whether HP-negative gastritis confers a similar increased risk for histologic progression to intestinal metaplasia and carcinoma. Furthermore, the etiology and clinical presentations of HP-negative gastritis remain poorly defined. This study aimed to assess the prevalence of HP-negative gastritis and characterize its demographic, clinical, and risk factor profile.

2. METHODS

A retrospective study was conducted on 241 consecutive patients referred for Esophagogastroduodenoscopy (EGD) at a single tertiary care center from July 2020 to July 2021. Patients were referred for EGD due to various upper gastrointestinal symptoms, including dysphagia, abdominal pain, nausea, vomiting, weight loss, iron deficiency anemia, bloating, belching, and Barrett's esophagus surveillance. Biopsy samples were taken from the gastric antrum and body during the EGD procedure. The study focused on evaluating the prevalence of Helicobacter pylori (HP)-negative gastritis and characterizing demographic, clinical, and risk factor profiles distinguishing HP-negative from H. pylori positive subjects with histologic gastritis.

Clinical, demographic, and laboratory data were collected and compared between HP-negative and HP-positive gastritis cases. The presence of medical co-morbidities, including specific conditions such as gastroesophageal reflux disease (GERD), was analyzed. Ethnicity, anatomic location of gastritis, and other relevant factors were also assessed.

3. RESULTS

3.1. Prevalence:
Among all patients (n=241), 38.2% (n=92) exhibited gastritis on biopsy. HP-negative gastritis accounted for 78% (n=71) of cases, while HP-positive gastritis accounted for 22% (n=20) (Table 1).

Table 1: Prevalence and histological classification of gastritis cases

	Gastritis Cases (n=92)	HP-Negative Gastritis (n=71)	HP-Positive Gastritis (n=20)
Prevalence	38.2%	78%	22%
Histological Types	-	Chronic Chemical: 61.5%	Active Chronic: 100%
		Chronic non-active: 33.2%	
		Active Chronic: 5.1%	

HP: Helicobacter pylori; n: number of patients.

3.2. Histological Characteristics:
In the HP-negative group, 61.5% had chronic chemical gastritis, 33.2% had chronic non-active gastritis, and 5.1% had active chronic gastritis. In the HP-positive group, all patients exhibited active chronic gastritis (Table 1).

3.3. Anatomic Distribution:
HP-negative gastritis predominantly affected antral biopsies (76.9%), differing significantly from HP-positive cases (antrum only: 36%, body: 36%, antrum and body: 27%, p=0.0162) (Table 2).

Table 2: Anatomic distribution and ethnic variation

	Anatomic Distribution	Ethnic Variation
HP-Negative Group	Antrum: 76.9% Body: 10.3% Antrum & Body: 12.8%	Caucasian: 61.5% African American: 20.5% Asian: 5.1%
HP-Positive Group	Antrum: 36% Body: 36% Antrum & Body: 27%	Middle Eastern: 2.6% Other: 10.3%
Ethnic Variation	p=0.0162*	p=0.0004* & p=0.0013*

HP: Helicobacter pylori; * Significant

3.4. Ethnic Variation:
Significant ethnic variation was observed, with HP-negative patients more likely to be Caucasian (61.5% vs. 0%) and HP-positive patients more likely to be African American (20.5% vs. 72.7%, p=0.0004 and p=0.0013, respectively) (Table 2).

3.5. Association with Medical Co-morbidities:
HP-negative gastritis was notably associated with medical co-morbidities compared to HP-positive gastritis (82.1% vs. 18.2%, p=0.0002). GERD was the most common co-morbidity associated with HP-negative gastritis (66.7% vs. 9.1%, p=0.0012) (Table 3).

Table 3: Association between medical co-morbidities and HP

	HP-Negative Gastritis (%)	HP-Positive Gastritis (%)
Medical Co-morbidities	82.1%	18.2%
GERD	66.7%	9.1%
Other Conditions	NA	NA
P-value	0.0002*	0.0012*

HP: Helicobacter pylori; GERD - Gastroesophageal Reflux Disease; NA: Not Applicable; *: Significant.

No significant differences were observed in predominant symptoms, primary referral indication, age, gender, prior HP infection, tobacco use, alcohol use, proton pump inhibitor (PPI) use, non-steroidal anti-inflammatory drug (NSAID) use, or antibiotic use.

4. DISCUSSION

Since the discovery and treatment of *H. pylori*, the prevalence of *H. Pylori* infection has been declining whereas HP-negative gastritis is becoming an increasingly recognized distinct entity. In one study by Nordenstedt *et al*., the prevalence of HP-negative gastritis was 21% in the study population, with a slight increase in prevalence in black males[13]. In another retrospective study, HP-negative chronic active gastritis was diagnosed in 12.7% of studied gastric biopsies with chronic active gastritis, and in 1.5% of the overall study population. There with a reported decline in prevalence from 2008 to 2014, and a slightly higher occurrence in females versus males [7]. Furthermore, Shiota *et al*. found that HP-negative gastritis was present in approximately 18% of patients

with gastritis and 9.9% in all study subjects with a higher prevalence amongst non-Hispanic whites [14]. In our study population, HP-negative gastritis was more prevalent among patients of Caucasian ethnicity whereas *H. pylori*-positive gastritis demonstrated increased prevalence amongst African American ethnicity.

Endoscopically, Chatrangsun *et al.* described gross findings of HP-negative gastritis mostly as a regular arrangement of collecting venules as well as fundic gland polyps, using white light imaging endoscopy, compared to diffuse redness and antral nodularity seen in patients with *H. pylori* positive gastritis via the same endoscopic modality [15]. Furthermore, with HP-negative gastritis, mucosal involvement was found to be more likely in isolated portions of the stomach, either body or antrum and, to a lesser extent, in both body and antrum. By comparison, 70% of patients with *H. pylori* positive gastritis had both body and antral distribution [13]. In patients with HP-negative gastritis, our findings demonstrated an overwhelming predominance of isolated antral involvement (76.9%). In patients with *H. pylori* positive gastritis, we did not find a predominance of concurrent antral and corpus involvement, nor did we find a predilection for isolated sites in this group.

Histologically, in those with HP-negative gastritis, the majority of cases demonstrated chronic chemical gastritis and chronic inactive gastritis (94.7%) whereas all cases of H. pylori gastritis demonstrated chronic active gastritis. These findings are similar to other published studies that demonstrate HP-negative gastritis to be chronic on histology [13, 14]. Importantly, histologic examination alone is insufficient to define HP-negative gastritis [14].

Data are lacking regarding common risk factors for HP-negative gastritis. Factors including smoking history, ETOH use, NSAID use, and recent PPI or H2 blocker use have been the focus of multiple studies. However, to the best of our knowledge, no studies have demonstrated a clinically significant correlation between these risk factors and HP-negative gastritis. In our study, medical co-morbidities were notably associated with HP-negative gastritis compared to *H. pylori* positive gastritis (82.1% vs. 18.2%, p=0.0002), with GERD being the most prevalent co-morbidity (66.7% vs. 9.1%, p=0.0012). However, this may be confounded by the fact that *H. pylori* infection exerts a protective effect against reflux [16].

HP-negative gastritis may be attributed to multiple causes. Some authors attribute HP-negative gastritis to an undetectable *H. pylori* organism [17], recently treated *H. pylori* infection, false negative *H. pylori* test, infectious gastritis due to organisms other than *H. pylori* such as cytomegalovirus, herpes simplex virus and Epstein-Barr virus or simply due to other non-infectious causes such as chemical gastritis, gastritis associated with inflammatory bowel disease or autoimmune gastritis [18]. The discrepancies in classifications and nomenclature in the literature can lead to confusion in identifying and studying HP-negative gastritis as a unique clinical entity. It is imperative to acknowledge that HP-negative gastritis may constitute a broad classification encompassing various sub-diagnoses, including *idiopathic chronic HP-negative gastritis* (in other words, "HP-negative gastritis" *proper*). El-Zimaty *et al*. detail a four-step diagnostic approach to cases of gastritis in which *H. pylori* is not identified[18]. Although this categorization was not adopted in our study, we believe this distinction should be made in future research.

This study has several limitations, including generalizability to the general population, given that all biopsy samples were obtained from a cohort in the United States. *H. pylori* false negative results are possible in the presence of PPI use, low bacterial load, and variations in gastric biopsy sampling methods.

5. CONCLUSION

In this retrospective study, the prevalence of HP-negative gastritis was 78% of those identified to have gastritis. HP-negative gastritis was significantly associated with medical co-morbidity and Caucasian ethnicity, with a preference for the antrum anatomically when compared with the H. pylori positive group. No statistically significant associations were identified with referral symptoms, PPI use, or other risk factors. Large-scale prospective studies are warranted to further elucidate the etiology, risk factors, pathogenesis, and clinical significance of this increasingly common entity.

Conflicts of Interest:
None

Ethical Approval:
None

Funding Source:
None

Acknowledgements:
None

Institutional Review Board (IRB) Approval:
This study was conducted with approval from the Institutional Review Board of the Faculty of Medicine, Cairo University, Cairo, Egypt. The approval was granted on September 15, 2021, with the IRB Approval Number: 34-5019824.

LLM Statement:
None

Authors Contribution Statement:
All authors have contributed equally to the conception, drafting, review, and final approval of this manuscript. Each author has read and agreed to the final version for publication.

Data Availability Statement:
Data from this study are not publicly available due to privacy concerns but can be obtained from the corresponding author upon request.

References

1. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996: 1161 [PMID: 8827022 https://doi.org/10.1097/00000478-199610000-00001]

2. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984: 1311 [PMID: 6145023 https://doi.org/10.1016/s0140-6736(84)91816-6]

3. Toyoshima O, Nishizawa T, Koike K. Endoscopic Kyoto classification of Helicobacter pylori infection and gastric cancer risk diagnosis. World J Gastroenterol. 2020: 466 [PMID: 32089624 https://doi.org/10.3748/wjg.v26.i5.466]

4. Li Y, Choi H, Leung K, Jiang F, Graham DY, Leung WK. Global prevalence of Helicobacter pylori infection between 1980 and 2022: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol.

2023: 553 [PMID: 37086739 https://doi.org/10.1016/S2468-1253(23)00070-5]

5. Sipponen P, Maaroos H-I. Chronic gastritis. Scandinavian Journal of Gastroenterology. 2015: 657 https://doi.org/10.3109/00365521.2015.1019918]

6. Ciociola AA, McSorley DJ, Turner K, Sykes D, Palmer JB. Helicobacter pylori infection rates in duodenal ulcer patients in the United States may be lower than previously estimated. Am J Gastroenterol. 1999: 1834 [PMID: 10406244 https://doi.org/10.1111/j.1572-0241.1999.01214.x]

7. Genta RM, Sonnenberg A. Helicobacter-negative gastritis: a distinct entity unrelated to Helicobacter pylori infection. Aliment Pharmacol Ther. 2015: 218 [PMID: 25376264 https://doi.org/10.1111/apt.13007]

8. Graham DY, Opekun AR, Hammoud F, Yamaoka Y, Reddy R, Osato MS, El-Zimaity HMT. Studies Regarding The Mechanism of False Negative Urea Breath Tests With Proton Pump Inhibitors. American Journal of Gastroenterology. 2003: 1005 https://doi.org/10.1111/j.1572-0241.2003.07426.x]

9. Laine L, Estrada R, Trujillo M, Knigge K, Fennerty MB. Effect of proton-pump inhibitor therapy on diagnostic testing for Helicobacter pylori. Ann Intern Med. 1998: 547 [PMID: 9758575 https://doi.org/10.7326/0003-4819-129-7-199810010-00007]

10. Genta RM. Where have all the Helicobacters gone? J Clin Gastroenterol. 2007: 727 [PMID: 17700419 https://doi.org/10.1097/MCG.0b013e3180684265]

11. Genta RM, Graham DY. Comparison of biopsy sites for the histopathologic diagnosis of Helicobacter pylori: a topographic study of H. pylori density and distribution. Gastrointest Endosc. 1994: 342 [PMID: 7794303 https://doi.org/10.1016/s0016-5107(94)70067-2]

12. Zsikla V, Hailemariam S, Baumann M, Mund MT, Schaub N, Meier R, Cathomas G. Increased rate of Helicobacter pylori infection detected by PCR in biopsies with chronic gastritis. Am J Surg Pathol. 2006: 242 [PMID: 16434900 https://doi.org/10.1097/01.pas.0000186397.18206.1b]

13. Nordenstedt H, Graham DY, Kramer JR, Rugge M, Verstovsek G, Fitzgerald S, Alsarraj A, Shaib Y, Velez ME, Abraham N, Anand B, Cole R, El-Serag HB. Helicobacter pylori-negative gastritis: prevalence and risk factors. Am J Gastroenterol. 2013: 65 [PMID: 23147524 https://doi.org/10.1038/ajg.2012.372]

14. Shiota S, Thrift AP, Green L, Shah R, Verstovsek G, Rugge M, Graham DY, El-Serag HB. Clinical Manifestations of Helicobacter pylori-Negative Gastritis. Clin Gastroenterol Hepatol. 2017: 1037 [PMID: 28110098 https://doi.org/10.1016/j.cgh.2017.01.006]

15. Chatrangsun B, Vilaichone RK. Endoscopic Diagnosis for H. pylori Infection: White Light Imaging (WLI) vs. Image-Enhanced Endoscopy (IEE). Asian Pac J Cancer Prev. 2021: 3031 [PMID: 34582676 https://doi.org/10.31557/APJCP.2021.22.9.3031]

16. Koike T, Ohara S, Sekine H, Iijima K, Kato K, Shimosegawa T, Toyota T. Helicobacter pylori infection inhibits reflux esophagitis by inducing atrophic gastritis. Am J Gastroenterol. 1999: 3468 [PMID: 10606305 https://doi.org/10.1111/j.1572-0241.1999.01593.x]

17. Genta RM, Lash RH. Helicobacter pylori-negative gastritis: seek, yet ye shall not always find. Am J Surg Pathol. 2010: e25 [PMID: 20631607 https://doi.org/10.1097/PAS.0b013e3181e51067]

18. El-Zimaity H, Choi WT, Lauwers GY, Riddell R. The differential diagnosis of Helicobacter pylori negative gastritis. Virchows Arch. 2018: 533 [PMID: 30255340 https://doi.org/10.1007/s00428-018-2454-6]