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Implantation of Bulking Agents for Faecal Incontinence

Update 2021
Systematic Review

AIHTA Decision Support Document: Nr. 87/1. Update 2021
ISSN-online: 1998-0469

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Vienna, March 2021

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This report should be referenced as follows:

Gassner L, Wild C. Implantation of Bulking Agents for Faecal Incontinence. AIHTA Decision Support Documents Nr. 87/1. Update 2021. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:
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AIHTA Decision Support Documents Nr. 87/1. Update 2021

ISSN online 1998-0469

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List of abbreviations

ACG ..... American College of Gastroenterology
AE ..... adverse events
AMS ..... American Medical Systems score
CCFIS ..... Cleveland Clinic Faecal Incontinence score
CRD ..... Centre for Reviews and Dissemination
d.h. ..... das heißt
DARE ..... Database of Abstracts of Reviews of Effects
DRG ..... Diagnosis Related Group
EAS ..... external anal sphincter

EUdraCT ..... European Union Drug Regulating Authorities Clinical Trials Database
EUnetHTA ..... European network for Health Technology Assessment
FDA..... Food and Drug Administration
FI..... faecal incontinence
FIQL ..... Faecal Incontinence Quality of Life score
FU ..... follow-up
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
h..... hours
HTA ..... Health Technology Assessment
HTA-INAHTA ..... International Network of Agencies for Health Technology Assessment
IAS..... internal anal sphincter
IBD..... inflammatory bowel diseases
ICD-10-CM ..... International Classification of Diseases, Tenth Revision, Clinical Modification
IHE..... Institute of Health Economics
IQR..... interquartile range
LKF..... Leistungsorientierte Krankenanstaltenfinanzierung
LQ ..... Lebensqualität
m..... mean
MUW ..... Medical University of Vienna
n..... number of patients/studies
NA ..... not available
NASHA ..... Non-Animal Stabilized Hyaluronic Acid
NHS-EED..... National Health Service – Economic Evaluation Database
NR ..... not reported
NS..... not significant
p.a ..... per annum
p.m..... per month
p.w. ..... per week
PRISMA..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTNS..... Posterior tibial nerve stimulation
pts ..... patients
QoL ..... quality of life
RCT..... randomised controlled trial
RoB..... risk of bias
s.s. ..... statistisch signifikant
SD..... standard deviation
SNS..... sacral nerve stimulation
SR ..... systematic review
stat. ..... statistisch
TAI ..... transanal irrigation
UK..... United Kingdom
USA ..... United States of America
WHO-ICTRP..... WHO International Clinical Trials Registry Platform
yrs ..... years

Executive Summary

Introduction

Health Problem

Faecal incontinence (FI), a common and highly prevalent condition, is the involuntary loss of intestinal contents due to an impaired ability to control the release of faeces or flatus. Patients suffer from complex health problems, causing considerable physical and psychosocial impairments leading to massive limitations in the quality of life (QoL). The prevalence is estimated to two to 20 per cent in the adult population, increases with age and is more common in women due to traumatic vaginal deliveries. FI can be caused by multifactorial reasons such as weak sphincter and pelvic floor muscles, injuries after surgery, medication, or psychological/mental disorders.

faecal incontinence (FI)

prevalence 2-20% in adults – increasing with age

complex multifactorial condition

Description of Technology

Only if conservative measures (e.g., pelvic floor exercises and biofeedback) fail, a minimally invasive surgical treatment is used: Anal bulking agents remain in the tissue and differ in the ingredients used and the particles' size. They aim to prevent FI by exerting increased pressure on the sphincter muscle. Implantable bulking agents (Gatekeeper™, Sphinkeeper™) are thin cylinders that change shape and size after 24 hours, resulting in improved continence.

implantable bulking agents as 2nd line therapy

Gatekeeper™, Sphinkeeper™

Methods

This systematic review aimed to investigate the use of implantable compared to injectable bulking agents in FI patients as second-line therapy after conservative measures failed. The question was whether implantable bulking agents are more effective and safe, concerning the outcomes of FI severity, disease-related QoL, and procedure and device-related adverse events.

systematic review on effectiveness (FI severity, QoL) and safety (adverse events)

The systematic search was conducted in five databases (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA], and HTA-INAHTA), limited to the years 2015 to 2020, and to articles published in English or German. Study designs were limited to randomised controlled trials (RCTs), prospective non-randomised controlled trials, and prospective case-series. The manufacturer submitted 15 publications, whereof one new citation was identified, resulting in overall 159 hits.

search in 5 databases
contact to manufacturer

159 publications

Results

Available evidence

The systematic search did not identify comparative trials, but six prospective, before-after, single-arm studies as best available evidence with a total of 143 analysed patients (median age range 20-80; 112 females). The studies were conducted between 2011 and 2018, and follow-up (FU) periods ranged between one and 36 months.

in total 143 pts in 6 prospective before-after, single-arm studies (2011-2018)

Clinical effectiveness

FI severity: significant improvement in 5 studies short and long term

FI severity, measured by the Cleveland Clinic Faecal Incontinence Score (CCFIS), significantly improved from baseline to 3-months ($p<0.0001$ and $p<0.01$) and 6-months ($p<0.05$) FU in five studies. Improvements in **severity's sustainability** (i.e., durability of efficacy >6 months) were reported after 12 ($p<0.01$), 14 ($p<0.01$), and 36 ($p<0.0001$) months postoperatively.

disease-related QoL: significant improvement only in 1 study

Improved **disease-related QoL**, measured by the Faecal Incontinence Quality of Life (FIQL) score, was found in only one study assessing lifestyle ($p<0.05$), coping/behaviour ($p<0.01$), depression/self-perception ($p<0.05$), and embarrassment ($p<0.01$) 12 months after surgery. One trial found significant improvements in **QoL's sustainability** after 12 months (lifestyle $p<0.05$, coping/behaviour and embarrassment $p<0.01$, depression/self-perception $p<0.05$).

Safety

procedure-related AE: 3/143 pts intraoperative complications, 11/143 pain etc

Procedure-related adverse events, such as intraoperative complications, occurred in three of 143 analysed patients, where prostheses extruded during surgery. Postoperative complications, morbidity, infection, sepsis, and inflammation did not occur. Eleven of 143 analysed patients felt anal discomfort, pain, and analgesia. Adverse effects, complications, and reactions did not occur in any patient.

device-related AE: 31/143 implant dislodgement

Device-related adverse events, e.g., dislodgement of prostheses, occurred in 31 patients and removed or extruded prostheses in three of 143 analysed patients.

Upcoming evidence

4 relevant studies ongoing (1 RCT)

A search in three clinical trials registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials [EUdraCT]) was conducted and yielded 13 hits, whereof four relevant studies, including one RCT, could be identified.

Discussion

findings:

improvement in FI severity, but not equally in QoL

objective vs subjective effects

This report aims to assess implantable bulking agents' clinical effectiveness and safety compared to injectable bulking agents, based on the best available evidence (prospective single-arm, before-after studies). The main finding is that the severity of FI significantly improved in five studies. The sustainability (i.e., durability of efficacy >6 months) of FI severity's improvement was observed in four studies after 12 to 36 months post surgery. Severity improvements did not show equal improvement in disease-related QoL. This may be because the same (objective) FI severity might affect individual patients on a different level, and the validation of the FIQL was only through translations.

dislodgement of prostheses in 22% of pts

more implants better than less

Device-related adverse safety events, such as dislodgement of prostheses, a common adverse event, occurred in nearly one-quarter of analysed patients. Displacements of bulking agents are the main cause of a possible progressive decline in a therapeutic effect. Comparing Sphinkeeper™ and Gatekeeper™, a higher number and greater size of Sphinkeeper™ prostheses aim to enhance the bulking effect, resulting in more significant improvements in symptom severity.

RoB: moderate to high quality of evidence: very low

Overall, the strength of evidence for clinical effectiveness outcomes was not assessed due to the lack of controlled trials. Regarding the safety of implantable bulking agents, the quality of evidence was very low. The overall risk of bias of the six included studies was moderate or high.

Conclusion

no comparative data but highly stigmatising condition most pts profit from conservative measures

In the absence of comparative data, it is not possible to ascertain the relative benefit and risk of implantable compared to injectable bulking agents. FI is a highly relevant topic, not only due to demographic changes but also because of its stigmatising impact on an individual's wellbeing. Fortunately, the majority of FI patients profit from conservative measures and the importance of these treatments must be highlighted.

implantable bulking agents: minimally invasive 2nd line therapy

Implantable bulking agents might be a minimally invasive approach in FI treatment if conservative therapies fail. They are still early in their development, and clinical implementation is only considered as second-line therapy. In the analysed studies, the severity of FI improved significantly but not so the QoL. This discrepancy needs to be explored in further studies.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Stuhlinkontinenz: häufige und weit verbreitete Erkrankung

komplexes Gesundheitsproblem, multifaktoriell bedingt

Stuhlinkontinenz, eine häufige und weit verbreitete Erkrankung, ist der unwillkürliche Verlust von Darminhalten. Der Schweregrad variiert zwischen ungewolltem Austritt von flüssigem Stuhl, Flatus oder der vollständigen Entleerung des Darminhaltes. Patient*innen mit Stuhlinkontinenz leiden unter einem komplexen Gesundheitsproblem, welches erhebliche körperliche und psychosoziale Beeinträchtigungen verursacht und zu massiven Einschränkungen der Lebensqualität aufgrund von Scham, Isolation und sozialer Ablehnung führt. Diese stigmatisierende und komplexe Erkrankung ist ein klinisches und soziales Problem.

stigmatisierend Tabuthema

Prävalenz: 2-20 % Zunahme mit Alter

Die Prävalenz wird auf zwei bis 20 Prozent in der erwachsenen Bevölkerung geschätzt und nimmt mit steigendem Alter zu. Die Prävalenz schwankt, abhängig von der verwendeten Definition von Stuhlinkontinenz und der Berücksichtigung verschiedener Alterskohorten. Die tatsächliche Zahl der Patient*innen ist nicht bekannt, da Stuhlinkontinenz ein Tabuthema ist, und selbst medizinisches Fachpersonal fällt es schwer darüber zu sprechen. Des Weiteren führt der demografische Wandel zu einer Zunahme der älteren Bevölkerung (>60 Jahre) und dementsprechend zu einer Zunahme der Indikation.

Ursachen:

schwacher Schließmuskel und/oder Beckenbodenmuskel, Verletzungen (Geburtstraumata)

Häufig wird Stuhlinkontinenz durch einen schwachen Schließmuskel und/oder Beckenbodenmuskel verursacht, jedoch auch Verletzungen, z. B. Hämorrhoiden oder Analfisteloperationen, können Stuhlinkontinenz verursachen. Funktionelle und strukturelle Anomalien des inneren und äußeren Schließmuskels treten bei Frauen häufiger auf, meist verursacht durch Geburtstraumata. Weitere Gründe können Medikamente, veränderte Stuhlkonsistenz, oder psychische, darmbezogene und neurologische Sensibilitätsstörungen sein. Die Auswahl geeigneter Behandlungen dieses heterogenen Problems stellt eine Herausforderung dar, aufgrund der multifaktoriellen Ätiologie, pathophysiologischen Mechanismen und der Schwierigkeit, die Ursache genau zu definieren. Bisher gibt es keinen Konsens zur Methodik der Klassifizierung der Symptome und Ursachen von Stuhlinkontinenz.

Beschreibung der Technologie

Therapie 1. Wahl: konservative Behandlungen

Mehrheit der Patient*innen spricht darauf an

Konservative Behandlungen, wie z. B. Beckenbodengymnastik, Verbesserung der Ernährungsgewohnheiten und medikamentöse Therapien, werden als Erstlinientherapie bei Stuhlinkontinenz eingesetzt. Die Mehrheit der Patient*innen spricht auf konservative Therapien an, wenn sie jedoch versagen stehen chirurgische Eingriffe als therapeutische Option zur Behandlung von Stuhlinkontinenz zur Verfügung. Eine minimalinvasive chirurgische Behandlung ist die Verwendung von analen Bulking Agents, welche seit über 25 Jahren eingesetzt werden. Anale Bulking Agents werden als Zweilinientherapie eingesetzt, wenn konservative Therapien versagt haben. Injizierbare und implantierbare Bulking Agents werden aus verschiedenen Biomaterialien angeboten, welche im Gewebe verbleiben und zur Verbesserung der Kontinenz beitragen. Injizierbare Bulking Agents werden in den Analkanal injiziert, um fäkale Inkontinenz zu verbessern.

Bulking Agents: Therapie 2. Wahl, minimalinvasiv injizierbar vs. implantierbar

Implantierbare Bulking Agents können als die neueste Generation analer Bulking Agents angesehen werden. Diese festen, dünnen Zylinder verändern 48 Stunden nach dem Einsetzen ihre Form und Größe und üben dadurch verstärkt Druck auf den Schließmuskel aus, was Stuhlinkontinenz verhindern kann. Implantierbare Bulking Agents werden als Gatekeeper™ und Sphinkeeper™ von der italienischen Firma THD s.p.A. hergestellt. Gatekeeper™-Implantate bestehen aus vier bis sechs Prothesen.

implantierbare Bulking Agents: Gatekeeper™ (4-6 Prothesen) und Sphinkeeper™ (10 Prothesen)

Das Material, Polyacrylnitril, ist nicht abbaubar/allergen und hat hydrophile Eigenschaften: Nach der Implantation im menschlichen Gewebe absorbieren die Zylinder innerhalb von 48 Stunden Feuchtigkeit und werden dadurch dicker, kürzer und weicher in der Konsistenz. Der Gatekeeper™ wurde zum Sphinkeeper™ modifiziert. Die höhere Anzahl an Implantaten (10 Prothesen) erreicht ein größeres Endvolumen an implantiertem Material, was den „Bulking-Effekt" erhöht. Sphinkeeper™, der weiterentwickelte künstliche Schließmuskel, ermöglicht somit die Behandlung schwerwiegender Defekte des inneren und äußeren Schließmuskels. Die Hauptindikation für den Einsatz von Gatekeeper™ und Sphinkeeper™ ist fäkale Inkontinenz, wenn konservative Maßnahmen oder Injektionen anderer Bulking Agents versagt haben.

Material: Polyacrylnitril

Prothesen sind Zylinder, die unter Feuchtigkeit dicker, kürzer und weicher werden = Bulking Effekt

Durch die Implantation der Prothesen zwischen inneren und äußeren Schließmuskel soll eine Migration oder Extrusion der Prothesen vermieden werden. Aufgrund der schnellen Zunahme an Volumen ist es weniger wahrscheinlich, dass sich die Implantate bewegen, da sie den inneren Schließmuskel nach innen und den äußeren Schließmuskel nach außen drücken. Das Operationsverfahren ist relativ einfach durchzuführen, allerdings können technische Probleme bei der Platzierung und dem Einsatz der Prothesen auftreten. Die Kosten für die Prothesen sind einmalig und Routinekontrollen sind selten.

Operationsverfahren: einfach, aber ev. Probleme bei Platzierung

Kosten: einmalig

Methoden

Das Ziel der vorliegenden Übersichtsarbeit ist es, implantierbare Bulking Agents (Intervention) mit injizierbaren Bulking Agents (Komparator) als Zweitlinientherapie für Stuhlinkontinenz bei Versagen konservativer Maßnahmen hinsichtlich des klinischen Nutzens und der Sicherheit zu vergleichen.

Ziel des SR: Nutzen und Risken im Vergleich zu injizierbaren Bulking Agents

Die systematische Literatursuche wurde am 17. Dezember 2020 in fünf Datenbanken (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA] und HTA-INAHTA) durchgeführt. Die systematische Suche wurde auf die Jahre 2015 bis 2020 und auf englische und deutsche Sprache beschränkt. Die Studiendesigns für die Wirksamkeit und Sicherheit von implantierbaren Bulking Agents wurden auf randomisierte kontrollierte Studien (RCTs), prospektive nicht-randomisierte kontrollierte Studien (nRCTs) und prospektive Vorher-Nachher-Studien beschränkt. Der Hersteller (THD s.p.A., Correggio, Italien) wurde kontaktiert und übermittelte 15 Publikationen, wovon eine neue Studie identifiziert wurde und in eine Gesamttrefferzahl von 159 Studien resultierte.

Suche in 5 Datenbanken

Kontakt zu Hersteller

159 Publikationen

Ergebnisse

Verfügbare Evidenz

6 prospektive Vorher-Nachher-Studien mit insg. 143 Patient*innen (2011-2018)

Die systematische Literaturrecherche identifizierte sechs prospektive, einarmige Vorher-Nachher-Studien, welche die Einschlusskriterien zur Beurteilung der klinischen Wirksamkeit und Sicherheit von implantierbaren Bulking Agents erfüllten. Alle Studien, bis auf eine (Spanien), wurden in Italien zwischen 2011 und 2018 durchgeführt. Die untersuchten Indikationen waren passive Stuhlinkontinenz in zwei Studien, Dranginkontinenz, passive und gemischte Stuhlinkontinenz in einer Studie, und drei Studien spezifizierten die Form der Stuhlinkontinenz nicht. Es wurden vier bis sechs Gatekeeper^{TM}- und zehn Sphinkeeper^{TM}-Prothesen implantiert.

7-54 Patient*innen pro Studie 20-80 Jahre

6 Patient*innen lost-to-FU

Insgesamt wurden 149 Patient*innen in diesen sechs Studien eingeschlossen und 143 analysiert: Sechs Patient*innen (aus einer Studie) konnten bei der Nachuntersuchung nicht untersucht werden. Alle Studien, mit Ausnahme von zwei, analysierten die Nachhaltigkeit von implantierbaren Bulking Agents, d. h. die Nachhaltigkeit der Wirksamkeit über mehr als sechs Monate. Die Anzahl der Patient*innen bei Studienbeginn schwankte zwischen sieben und 54 Patient*innen zwischen 20 und 80 Jahren.

Analyse von kurz- und langfristigen Effekten

Klinische Wirksamkeit

Schweregrad der Stuhlinkontinenz gemessen mit CCFIS (und/oder Vaizey)

Der **Schweregrad der Stuhlinkontinenz**, gemessen mit dem Cleveland Clinic Faecal Incontinence Score (CCFIS), verbesserte sich in fünf Studien und eine Studie berichtete keine postoperativen Daten. Eine signifikante Verbesserung des Schweregrades konnte bei den Untersuchungen nach drei ($p<0,0001$ und $p<0,01$), sechs ($p<0,05$), zwölf ($p<0,01$ und $p<0,001$), 14 ($p<0,01$) und 36 Monaten ($p<0,000$) nach der Implantation, verglichen zur präoperativen Messung, festgestellt werden.

signifikante Verbesserung in 5 von 6 Studien

1 Studie: keine postoperativen Daten

Der Vaizey-Score verbesserte sich in zwei von drei Studien; eine Studie berichtete keine postoperativen Daten. Der Schweregrad verbesserte sich nach zwölf ($p<0,001$) und 14 Monaten ($p<0,01$) nach der Operation.

Nachhaltigkeit der Effekte (>6 Monate) in 4 von 6 Studien gemessen: anhaltend signifikante Verbesserung

Vier Studien berichteten über die **Nachhaltigkeit** der implantierbaren Bulking Agents, d. h. die nachhaltige Wirksamkeit über mehr als 6 Monate, in Bezug auf den **Schweregrad** der Stuhlinkontinenz. Verbesserungen, gemessen mit dem CCIFS, wurden nach zwölf ($p<0,01$), 14 ($p<0,01$) und 36 ($p<0,0001$) Monaten nach der Operation berichtet. Zwei Studien verwendeten zusätzlich den Vaizey-Score. Hier verbesserte sich der Schweregrad der Stuhlinkontinenz signifikant nach zwölf ($p<0,001$) und 14 ($p<0,01$) Monaten nach der Operation.

krankheitsbezogene Lebensqualität gemessen mit FIQL (und/oder AMS)

Die krankheitsbezogene **Lebensqualität**, gemessen mit der Faecal Incontinence Quality of Life Scale (FIQL), verbesserte sich in zwei von vier Studien nicht signifikant; eine Studie berichtete keine postoperativen Daten. Eine Verbesserung der Lebensqualität konnte in einer Studie zwölf Monate nach der Operation in den Bereichen Lebensstil ($p<0,05$), Bewältigung/Verhalten ($p<0,01$), Depression/Selbstwahrnehmung ($p<0,05$) und Verlegenheit ($p<0,01$) festgestellt werden.

signifikante Verbesserung nur in 1 Studie

Der American Medical Systems (AMS) Score wurde in zwei Studien zusätzlich eingesetzt. Die Lebensqualität verbesserte sich nach zwölf Monaten signifikant ($p<0,001$). In der zweiten Studie wurden keine postoperativen Daten berichtet.

Zwei Studien berichteten über die **Nachhaltigkeit** implantierbarer Bulking Agents in Bezug auf die krankheitsbezogene **Lebensqualität**. Signifikante Verbesserungen der Lebensqualität konnten nach zwölf Monaten, gemessen mit dem FIQL, beobachtet werden (Lebensstil $p<0,05$, Bewältigung/Verhalten und Verlegenheit $p<0,01$, Depression/Selbstwahrnehmung $p<0,05$), sowie beim AMS ($p<0,001$). Die zweite Studie zeigte keine statistisch signifikanten Unterschiede in der Lebensqualität, gemessen mit den FIQL, zwölf Monate nach der Operation.

ebenso: kurz- wie langfristige Verbesserung in nur 1 Studie

Sicherheit

Unerwünschte Ereignisse bezüglich des **Operationsverfahrens** wurden in vier von sechs Studien hinsichtlich intraoperativer Komplikationen berichtet: In drei von 143 analysierten Patient*innen extrudierten Prothesen während der Operation. Postoperative Komplikationen und Morbidität sowie Infektionen, Sepsis und Entzündungen wurden in fünf Studien berichtet, traten jedoch in keiner dieser Studien auf. Analbeschwerden, Schmerzen und Analgesie wurden in fünf Studien berichtet, in welchen elf von 143 analysierten Patient*innen davon berichteten. Unerwünschte Wirkungen, Komplikationen und Reaktionen wurden in drei Studien berichtet, traten jedoch bei keiner/keinem Patient*in auf.

intraoperative Komplikationen: 3/143 Patient*innen

postoperative Komplikationen (Schmerz etc.): 11/143 Patient*innen

Hinsichtlich **gerätebezogener** unerwünschter Ereignisse wurde in allen sechs Studien über eine Dislokation von Prothesen berichtet, welche bei 31 von 143 analysierten Patient*innen auftrat. Bei drei von 143 analysierten Patient*innen wurden Prothesen entfernt oder extrudiert, was in drei Studien berichtet wurde.

Prothesen-bezogene Ereignisse: Dislokation von 31/143 (22 %), mussten aber nur bei 3 entfernt werden

Laufende Studien

Eine Suche in drei Registern für klinische Studien (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials [EUdraCT]) wurde durchgeführt und erbrachte 13 Treffer. Davon konnten vier relevante laufende Studien, die Bulking Agents untersuchen, identifiziert werden: Drei Beobachtungsstudien mit kleiner Patient*innen-Anzahl und eine randomisiert kontrollierte Studie vergleicht Anal Bulking Agents vs. Sakralnervenstimulation.

Suche in drei Registern zu laufenden Studien: 3 Beobachtungsstudien + 1 RCT

Diskussion

Nach Versagen konservativer Maßnahmen können Bulking Agents als letzte minimalinvasive Option in der Behandlung der Stuhlinkontinenz angesehen werden. Dieser Update-Bericht 2021 zielt darauf ab, die klinische Wirksamkeit und Sicherheit von implantierbaren Bulking Agents, eine minimalinvasive Zweitlinientherapie nach Versagen konservativer Maßnahmen, im Vergleich zu injizierbaren Bulking Agents zu bewerten. Die Mehrheit der Stuhlinkontinenz-Patient*innen profitiert von konservativen Maßnahmen. In einer Übersichtsarbeit mit 574 Patient*innen waren nur bei neun Prozent chirurgische Eingriffe erforderlich. Daher muss die Bedeutung konservativer Maßnahmen bei Stuhlinkontinenz hervorgehoben werden.

Bulking Agents als Zweitlinientherapie nach Versagen von konservativen Therapien

Bericht 2015: injizierbare Bulking Agents

Der ursprüngliche Bericht von 2015 befasste sich mit injizierbaren Bulking Agents basierend auf einem Cochrane-Review aus dem Jahr 2013. Da es sich bei implantierbaren Bulking Agents (Gatekeeper™ und Sphinkeeper™) um relativ neue Techniken handelt, ist dieser Bericht – unseres Wissens – die erste systematische Übersichtsarbeit, welche auf der besten verfügbaren Evidenz (prospektive, einarmige Vorher-Nachher-Studien) basiert. Gatekeeper™-

Update-Bericht 2021: injizierbare vs. implantierbare Bulking Agents; Gatekeeper™ und Sphinkeeper™; CE-Zertifizierung 2010

und Sphinkeeper™-Implantate haben bereits 2010 das CE-Kennzeichen der Medizinprodukterichtlinie erhalten und (unter der neuen Medizinprodukteverordnung) wurde eine Revision im Jahr 2020 durchgeführt.

Zusammenfassung der Evidenz

best verfügbare Evidenz: 6 prospektive Vorher-Nachher-Studien mit insg. 143 Patient*innen

Die systematische Literaturrecherche identifizierte keine vergleichenden Studien, sondern nur sechs prospektive, einarmige Vorher-Nachher-Studien als beste verfügbare Evidenz mit insgesamt 143 analysierten Patient*innen (Alter: 20-80 Jahre; 112 Frauen; 81 Patient*innen: Gatekeeper™; 62 Patient*innen: Sphinkeeper™). Von diesen sechs Studien wurden fünf in Italien und eine in Spanien durchgeführt (single-center: fünf; multi-center: eine Studie). Die Patient*innen wurden mit jeweils vier bis sechs Gatekeeper™-Prothesen oder zehn Sphinkeeper™-Prothesen behandelt. Die Zeiträume der Nachbeobachtungen lagen zwischen einem und 36 Monaten.

5 davon in Italien 4-6 Gatekeeper™- oder 10 Sphinkeeper™-Prothesen pro Patient*in

Klinische Wirksamkeit und Sicherheit

Ergebnis:

in 5 Studien klinisch relevante Verbesserungen im FI-Schweregrad

Das wichtigste Ergebnis dieses Berichtes ist, dass sich der Schweregrad der Stuhlinkontinenz (gemessen mit dem CCFIS und/oder Vaizey Score) in fünf Studien, welche prä- und postoperative Daten analysierten, signifikant verbesserte. In dieser Übersichtsarbeit konnten klinisch relevante Verbesserungen des Schweregrades, d. h. eine mindestens 50 %ige Reduktion im Vergleich zu den präoperativen Daten, nach drei, sechs, zwölf und 14 Monaten beobachtet werden. Hinsichtlich der Anzahl der Episoden konnte die klinisch relevante Verbesserung in einer Studie nach drei und zwölf Monaten gezeigt werden. Die Nachhaltigkeit der Verbesserung des Schweregrades, d. h. Nachhaltigkeit der Wirksamkeit von über sechs Monaten, wurde in vier Studien nach zwölf, 14 und 36 Monaten postoperativ beobachtet.

kurzfristige und nachhaltige Verbesserungen

jedoch keine äquivalenten Verbesserungen der krankheitsbezogenen Lebensqualität

Erstaunlicherweise zeigten diese Verbesserungen des Schweregrads der Stuhlinkontinenz nicht die gleichen Verbesserungen in der krankheitsbezogenen Lebensqualität (gemessen mit FIQL und/oder AMS): Nur in einer Studie verbesserte sich die Lebensqualität signifikant. Dies könnte daran liegen, dass derselbe (objektive) Schweregrad der Stuhlinkontinenz einzelne Patient*innen auf einem unterschiedlichen Niveau beeinträchtigen könnte und die Validierung des FIQL nur durch Übersetzungen erfolgte. Nichtsdestotrotz erfüllt der FIQL die psychometrischen Kriterien für Validität und Reliabilität und wird für die Beurteilung der Lebensqualität bei Stuhlinkontinenz empfohlen.

nur 1 Studie berichtet signifikante Verbesserung der LQ

unerwünschte Ereignisse: Dislokation bei 22 % der Patient*innen

Sicherheitsaspekte wurden in Form von unerwünschten Ereignissen bezüglich des Operationsverfahrens und der verwendeten Geräte (implantierbare Bulking Agents) berichtet. Eine Verschiebung von Prothesen trat bei fast einem Viertel der analysierten Patient*innen auf und ist ein häufiges, unerwünschtes Ereignis, welches in 14 bis 71 Prozent der Fälle auftritt. Solche Verschiebungen von Implantaten sind die Hauptursache für einen möglichen progredienten Rückgang der therapeutischen Wirksamkeit. Dennoch korrelieren Prothesenverschiebungen negativ mit postoperativen Veränderungen des Stuhlinkontinenz-Schweregrades, gemessen mit CCFIS, nach zwölf Monaten.

NICE-Assessment 2020: Evidenz unzureichend, nur in Studien anzuwenden

Das Nationale Institut für Gesundheit und Qualität (NICE) kam 2020 zu dem Schluss, dass die Evidenz zur Sicherheit und Wirksamkeit von Implantaten in den Raum zwischen den Schließmuskeln bei Stuhlinkontinenz qualitativ und quantitativ unzureichend ist. Daher sollte dieses Verfahren nur im Rahmen von Studien eingesetzt werden.

Gatekeeper™ vs. Sphinkeeper™

2 Vergleichsstudien: Sphinkeeper™ vs. Gatekeeper™ (weniger vs. mehr Prothesen) ev. mehr Prothesen effektiver

In einer Studie wurde ein Vergleich zwischen den beiden Produkten Sphinkeeper™ und Gatekeeper™ durchgeführt. Zehn Patient*innen erhielten je zehn Sphinkeeper™-Prothesen und wurden altersmäßig mit zehn Patient*innen, die je sechs Gatekeeper™-Prothesen erhalten hatten, gematcht. In dieser vergleichenden Analyse zeigte sich die Überlegenheit der Verwendung einer größeren Anzahl von Prothesen. Der Schweregrad der Symptome verbesserte sich signifikant in beiden Gruppen zwölf Monate nach der Operation, jedoch war die Verbesserung bei den Sphinkeeper™-Patient*innen um ein Drittel größer. In einer anderen Studie zeigten die Patient*innen einer Subgruppenanalyse (4 vs. 6 Prothesen bei 20 Patient*innen) bessere Ergebnisse nach der Implantation von sechs Prothesen. Diese beiden Ergebnisse legen nahe, dass mehr Prothesen effektiver sein könnten und Patient*innen mit vorangeschrittener Stuhlinkontinenz mehr von Sphinkeeper™-Implantaten profitieren könnten.

Interne und externe Validität

Mangel an kontrollierten Studien

niedrige Qualität der Evidenz
RoB: moderat bis hoch

zahlreiche Limitationen

Die Stärke der Evidenz für die klinischen Wirksamkeitsergebnisse konnte aufgrund des Mangels an kontrollierten Studien nicht bewertet werden. Bezüglich der Sicherheit implantierbarer Bulking Agents war die Qualität der Evidenz sehr gering. Limitationen der verfügbaren Evidenz müssen berücksichtigt werden: Bei den sechs eingeschlossenen prospektiven Vorher-Nachher-Studien war das Risiko einer Verzerrung insgesamt moderat (n=3) oder hoch (n=3). Die wichtigste Einschränkung ist vor allem, dass alle eingeschlossenen Studien aufgrund ihres unkontrollierten Vorher-Nachher-Studiendesigns sehr anfällig für Verzerrungen sind. Eine weitere wichtige Limitation ist, dass alle klinischen Endpunkte direkt von den Patient*innen berichtet wurden. Diese subjektiven Endpunkte beinhalten ein hohes Risiko für Berichtsverzerrungen, auch wenn validierte Fragebögen verwendetet wurden. Weitere Bedenken waren das single-center Design in fünf Studien, fehlende Patientencharakteristika, unterschiedliche Krankheitsstadien der Patient*innen zu Beginn der Studie und, dass die Sudienergebnisse nicht verblindet bewertet wurden. In Bezug auf die Sicherheit könnte die geringe Patient*innen-Anzahl in den Studien (7-54 Patient*innen) das Auftreten von (seltenen schweren) unerwünschten Ereignissen beeinflusst haben.

Limitationen

vorab definierte Endpunkte berücksichtigen weitere Endpunkte nicht ausreichend

keine Subgruppenanalysen

Die vorab definierten Endpunkte (Stuhlinkontinenz-Schweregrad, krankheitsbezogene Lebensqualität, Nachhaltigkeit und Sicherheit) repräsentieren die wichtigsten klinischen Therapieziele, welche in allen eingeschlossenen Studien standardisiert analysiert wurden. Andere patientenrelevante Endpunkte, wie die Aufschiebung der Stuhlentleerung und Subgruppenanalysen, z. B. der Einfluss von Geburtstraumata, wurden in diesem Bericht nicht berücksichtigt, da diese Endpunkte auch im Bericht von 2015 nicht analysiert wurden.

Conclusio

keine Vergleichsdaten = keine Beurteilung des relativen Nutzens möglich

In Ermangelung von Vergleichsdaten ist es nicht möglich, den relativen Nutzen und das Risiko von implantierbaren im Vergleich zu injizierbaren Bulking Agents zu bewerten. Stuhlinkontinenz ist ein hochrelevantes Thema, nicht nur aufgrund des demografischen Wandels, sondern auch wegen der stigmatisierenden Auswirkungen auf das Wohlbefinden des Einzelnen.

Stuhlinkontinenz ist relevantes Thema, auch wegen demografischem Wandel

Implantierbare Bulking Agents können ein minimalinvasiver Ansatz in der Behandlung von Stuhlinkontinenz sein, wenn konservative Therapien versagen. Implantierbare Bulking Agents befinden sich noch in einem frühen Entwicklungsstadium und der klinische Einsatz wird als Zweitlinientherapie in Betracht gezogen. In den analysierten Studien verbesserte sich der Schweregrad der Stuhlinkontinenz signifikant, nicht aber die Lebensqualität. Diese Diskrepanz soll in weiterführenden Studien untersucht werden.

Empfehlung

junge Technik in frühem Anwendungsstadium

Stuhlinkontinenz ist eine belastende Erkrankung, welche die Lebensqualität der Betroffenen erheblich beeinträchtigt. Die vorliegende best verfügbare Evidenz zeigt, dass sich die bewertete Technologie, implantierbare Bulking Agents (Gatekeeper™ und Sphinkeeper™), noch in einem frühen Anwendungsstadium befindet (143 Patient*innen wurden in einarmigen Studien analysiert). Implantierbare Bulking Agents sind jedoch vielversprechend, den Schweregrad der Stuhlinkontinenz zu verbessern und stellen eine relativ sichere Behandlung dar.

nur in klinischen Studien oder unter Dokumentation

Trotz der begrenzten Evidenz der eingeschlossenen Studien (d. h. keine kontrollierten Studien) werden implantierbare Bulking Agents bei Stuhlinkontinenz mit Einschränkungen – nur in klinischen Studien und/oder in spezialisierten Zentren unter Dokumentation – für ausgewählte Patient*innen empfohlen.

Summary of previous assessment 2015

Zusammenfassung von MEL aus 2015

Fokus 2015: injizierbare Bulking Agents

This chapter summarises the results of the decision support document Nr. 87 (2015) entitled 'Injectable bulking agents for faecal incontinence'. The systematic review from 2015 aimed to evaluate injectable bulking agents' efficacy and safety compared to conservative therapies and other bulking agents [1]. For faecal incontinence (FI) treatment, injectable bulking agents are used in adults who suffer from passive FI and if physiological conditions, i.e., weak but intact internal anal muscle, are present. The therapeutic objective is primarily to prevent FI episodes and to improve the quality of life (QoL) in FI patients [1].

PICO 2015

Table 1: Inclusion criteria 2015

Population	Adult patients (≥18 yrs) with passive faecal incontinence
Intervention	Bulking Agents – injections
Control	■ conservative therapies ■ (other) Bulking Agents
Outcomes	
Efficacy	■ Incontinence episodes ■ Health-related (in)continence responsible quality of life scores, e.g., ■ Cleveland Clinic Faecal Incontinence Score ■ Faecal Incontinence Quality of Life Scale ■ St Mark's (Incontinence) Score ■ Wexner Score ■ Sustainability of interventions (durability of efficacy) >6 months
Safety	Postoperative complications (e.g., bleeding, infections, injection site or anal pain or discomfort, new evacuation difficulty)
Study design	
Efficacy	Randomised controlled trials
Safety	Randomised controlled trials Observational studies (according to Cochrane Review [2])

Results

SR 2015 basierte auf Cochrane Review 2013

ingesamt 7 RCTs mit 543 Pts, davon erhielten 304 Pts Bulking Agents

The systematic review 2015 [1] was based on a Cochrane review from 2013 with the identical research question on bulking agents' superiority over conservative therapies [2]. The systematic literature search identified seven randomised controlled trials (RCTs) [3-9], of which two [3, 4] had not been assessed in the Cochrane review [2]. These seven RCTs included 543 patients, of which 304 patients received the interventions (injectable bulking agents). The following injectable bulking agents products were used in the RCTs: Solesta®, Bulkamid™, PTQ™, Durasphere®, and Permacol™.

Effectiveness and safety of injectable bulking agents for faecal incontinence

keine Überlegenheit von injizierbaren Bulking Agents gegenüber konservativen Therapieansätzen und anderen Bulking Agents

Altogether, the evidence did not demonstrate the superiority of injectable bulking agents compared with conservative therapy. In addition, no consensus about the choice of an optimum bulking agent exists. Solesta® showed in one RCT significant improvements in the 6-months follow-up (FU) concerning reduced incontinence episodes compared with a sham injection. However, no significant differences were found in an RCT comparing Solesta® and biofeedback [1].

deutlich mehr Nebenwirkungen in Interventionsgruppe

In five of seven RCTs, safety endpoints were insufficiently documented. In one study, the most common adverse event was proctalgia, with 19 events in the intervention group and two in the control group. Two events in the intervention group were described as severe (two cases of abscesses). Most side effects were reported in an RCT dealing with Solesta® [1].

Conclusion

niedrige Evidenz (trotz RCTs) deutet auf keinen Nutzen hin

The available (low) evidence points out that patients with passive FI did not benefit more from injectable bulking agents than from standard therapy. The relevance of the primary endpoint for patients (≥50% reduction of incontinence episodes) was contested. Against this backdrop, robust RCTs and further research are needed to gain substantial evidence about long-term outcomes such as QoL [1].

robuste Langzeitstudien notwendig

Recommendation 2015

keine Aufnahme in den Leistungskatalog empfohlen

The inclusion in the catalogue of benefits was not recommended in 2015. The available evidence suggested that injectable bulking agents were not more effective and safer than conservative treatments in adult patients with passive FI. Furthermore, it was stated that there was no superiority of substances or products among the different injectable bulking agents [1].

UPDATE 2021

1 Background

1.1 Overview of the disease, health condition and target population: Faecal incontinence

Stuhlinkontinenz (FI) verursacht nicht nur physisches, sondern auch psychisches und soziales Leiden

Faecal incontinence (FI), a common and highly prevalent condition, is the involuntary loss of intestinal contents due to an impaired ability to control the release of faeces or flatus [1, 10-13]. Patients with FI suffer from a complex health problem causing considerable physical and social impairments leading to massive limitations in the quality of life (QoL) due to isolation, shame, and social rejection [1]. This stigmatising and complex condition adversely affects psychological wellbeing [13-16].[1, 2, 3]

unterschiedliche Schweregrade

akute, passive und gemischte Formen der FI

FI severity varies from the escape of liquid faeces, unintentional leak of flatus, or complete evacuation of bowel contents [15]. An urge, passive, and mixed form of FI are published [1]:

- In urge FI, patients recognise signs of an imminent stool discharge, but no toilet can be visited due to sudden onset.
- Passive FI is recognised after stool discharge with no or less previous indices.

Schwäche der Analmuskulatur

Urge FI indicates a weak function of the external anal sphincter (EAS), whilst passive FI is suggestive of a poor internal anal sphincter (IAS) [13].

Prävalenz: 2-20 % der Erwachsenen; Zunahme mit Alter; unterschiedliche Definitionen

The prevalence is estimated to 2-20% in the adult population and increases with age [15, 16], with adverse effects on QoL and a high societal impact [10-12]. Prevalence ranges, depending on the definition used [1, 17] and on the consideration of different age cohorts [1].[4]

unterschätze Prävalenz: Tabuthema, klinisches UND soziales Problem

FI is a clinical *and* social problem [10]. The real number of patients is unknown because FI is still a taboo subject [18], and even health professionals find it hard to talk about [17]. Further, demographic change leads to an increase in the elderly population (>60 yrs), which is expected to increase by 7-10% until 2030 [19].[5]

Ursachen: Gebärtraumata, Verletzungen nach operativen Eingriffen, Medikamente, neurologische Ursachen etc.

Functional and/or structural abnormalities of the EAS and IAS are more common in women, mostly caused by obstetric traumas [14] (ratio 80 (females) : 20 (males) [20]).[6] Commonly, FI is caused by a weak sphincter muscle and/or pelvic floor muscle. Also, injuries, e.g., haemorrhoids or anal fistula surgeries, can cause FI [1]. Further reasons can be medication, modified stool consistency, mental, bowel, neurological, intestinal motility or sensory disor-

[1] A0001 – For which health conditions, and for what purposes are implantable bulking agents used?

[2] A0002 – What is the disease or health condition in the scope of this assessment?

[3] A0005 – What is the burden of disease for the patients with faecal incontinence?

[4] A0023 – How many people belong to the target population?

[5] A0006 – What are the consequences of implantable bulking agents for the society?

[6] A0023 – What is the target population in this assessment?

ders [1, 18]. The choice of appropriate treatments can be challenging due to the i) multifactorial aetiology, ii) pathophysiological mechanisms, iii) and difficulty in accurately defining the cause [12, 15, 21, 22]. The following groups at high risk of FI can be defined [17]:[7]

Pts-Gruppen: hochbetagte Pts, Frauen nach Geburten, Pts mit Rückmarksverletzungen, Pts mit kognitiven Beeinträchtigungen, Pts nach Eingriffen am Darm

- Frail older people
- Women after delivery
- Patients with diarrhoea or loose stools
- Patients with spinal cord injury or neurological disease
- Patients with learning disabilities or severe cognitive impairments
- Patients with perianal soreness, itching or pain, urinary incontinence, pelvic organ or rectal prolapse
- Patients after colonic resection, pelvic radiotherapy or anal surgery

In the complex management of FI, a multidisciplinary treatment team is involved: general practitioner, continence nurse, gastroenterologist, physiotherapist, colorectal surgeon, and urologist [13].[8]

1.2 Current clinical practice: Conservative measures

konservative Therapien = Erstlinientherapien:

Different treatment options are available, while conservative therapy always precedes more invasive treatments [1]. Conservative measures are defined as non-invasive and non-surgical interventions, preventing further declines or improving FI symptoms [23]. This first-line therapy includes [11, 13, 15]:

Pts-Aufklärung zu Ernährungsgewohnheiten, Beckenbodentraining, Einlagen, Biofeedback, Elektrostimulation

- Patient support and education
- Bowel and diet habits
- Pelvic floor exercises
- Anti-diarrhoeal medication
- Biofeedback
- Inserts and plugs
- Electrical stimulation

abgestuftes Vorgehen Langzeiterfolge?

etwa 50 % der Pts sprechen auf konservative Therapien an

Usually, treatments are delivered in a stepwise manner, i.e., conservative treatments followed by more invasive interventions [11]. Among conservative treatment options, the sustainability of interventions, i.e., duration of symptom improvement, is challenging [1, 23] as they often do not represent long-term solutions with high failure rates [1, 16]. Despite this, almost half of the patients respond well to conservative therapies, but if these therapies fail, alternatives such as implantable bulking agents are second-line options [10].

[7] A0003 – What are the known risk factors for faecal incontinence?

[8] B0004 – Who administers implantable and injectable bulking agents and in what context and level of care are they provided?

1.2.1 Clinical guidelines[9] and more invasive procedures

Stuhlinkontinenz häufiges, aber heterogenes Problem

FI (ICD-10-CM Code R15) is a heterogeneous problem that ranges from minor faecal soiling to incapacitating urge or passive FI. However, a common and highly prevalent condition, no European guidelines on the management of FI could be identified. There is no consensus on methods of classifying the symptoms and causes of FI. It is most commonly classified according to symptoms, the character of the leakage, patient group, or presumed primary underlying cause [24].

kein Konsens zur Methodik der Klassifizierung

klinische Leitlinien der ACG 2014 zum Management von FI: Abklärung der Ursache

The algorithm (Figure 1-1) published in 2014 in the clinical guideline of the American College of Gastroenterology (ACG) on the management of FI suggests the evaluation and management of FI by starting with the clinical evaluation (including a digital rectal examination). In this first screening, a perianal inspection analyses the defaecatory disorders' causes (rated as low quality of evidence and a weak recommendation) [25]. Initial management of FI includes interventions related to diet, bowel habit and toilet access, and medication.

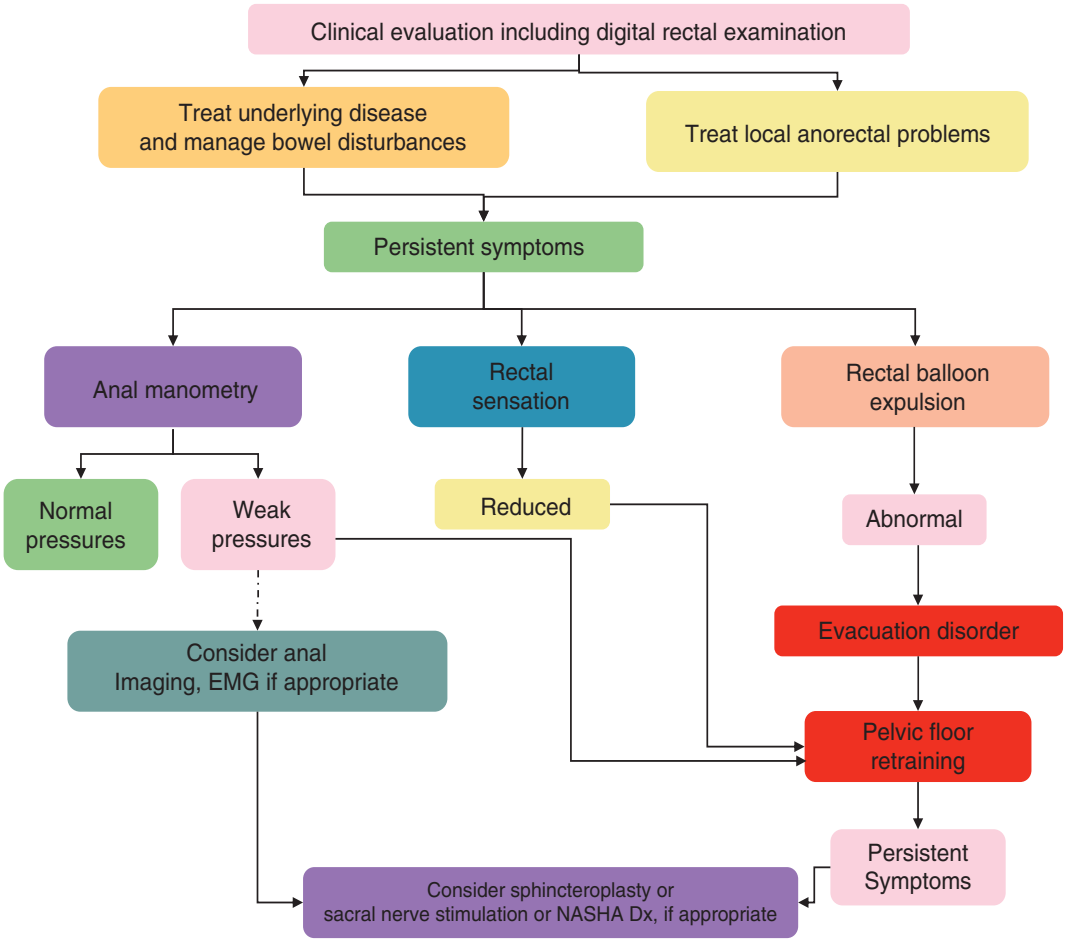


Figure 1-1: Suggested algorithm for diagnosis and management of faecal incontinence. Source: [25]

[9] A0024 – How is faecal incontinence currently diagnosed according to published guidelines and in practice?

therapeutisches Management von Ursachen abhängig: chirurgische Interventionen erst nach konservativen Ansätzen

Specialised management options depend on the underlying cause and include pelvic floor muscle training, bowel retraining, specialist dietary assessment and management, biofeedback, electrical stimulation and rectal irrigation. Sacral nerve stimulation (SNS) may be offered to people for whom sphincter surgery is not appropriate. If an SNS trial is unsuccessful, a neosphincter may be considered (stimulated graciloplasty or an artificial anal sphincter). The main surgical treatment is anal sphincter repair [24].

Further, injectable bulking agents (NASHA® Dx) can be considered. If measures such as dietary adjustments, injectable or implantable bulking agents fail, more invasive procedures are available [23].

As the guideline dates from 2014, and the implantable products are not approved in the US, they are not mentioned in this guideline [25].

bei schwerer FI können auch invasive Methoden zum Einsatz kommen

The 'International Consultation in Incontinence' (an expert panel of incontinence specialists) proposed a treatment algorithm for FI, following a stepwise approach of possible invasive treatments if minimally invasive treatments, e.g., bulking agents, fail [26]. The following describes the management algorithm pyramid (Figure 1-2):

Transanale Irrigation (TAI)

- **Transanal irrigation (TAI):** Transanal irrigation aims at emptying the descending and rectosigmoid colon using specialised catheters. Usually, the patients administer the enema daily. Half of the patients show successful outcomes after 21 months [23].

Sakralnervenstimulation (SNS)

- **Sacral nerve stimulation (SNS):** At this surgical procedure, an electrode placed at vertebra S3 stimulates the sacral nerve roots. This stimulation effectively reduces FI episodes with high rates of success and good long-term results [23]. However, according to a systematic review by the Cochrane Collaboration, the clinical effectiveness of SNS in treating patients with passive FI is not yet conclusively clarified [2]. SNS can be seen as an effective approach for FI conditions, but it is a lifelong journey, and it is expensive [11].

perkutane tibiale Nervenstimulation (PTNS)

- **Posterior tibial nerve stimulation (PTNS):** Here, needle electrodes are used for percutaneously stimulating the posterior tibial nerve. Stimulation sessions range from daily to once per week [23].

Sphinkteroplastie

- **Sphincter reconstruction:** Sphincteroplasty aims at reconstructing defects in the EAS. Short-term improvements have been reported in up to 86% of FI patients, but after 5-10 years, only 25-40% are continent [23].

antegrade Irrigation

- **Antegrade irrigation:** At this method, scheduled controlled emptying of the colon avoids FI. Long-term results show a success rate of around 75% [23].

weitere chirurgische Interventionen:

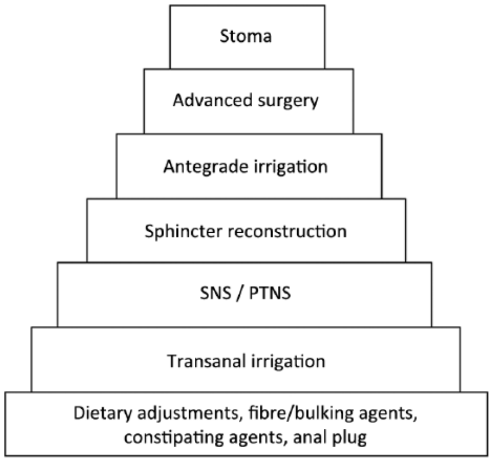
dynamische Gracilisplastik

Radiofrequenztherapie

- **Advanced surgery:** Advanced surgical methods should be performed at specialist centres, restricted to highly selected patients. For the *dynamic graciloplasty*, a neosphincter procedure, a magnetic anal sphincter or an artificial bowel sphincter is implanted. Graciloplasty aims at creating a new splinter around the anus using the patient's gracilis muscle. An electrode sustains the muscle tone. Success rate range from 42-85%, and complications are common. *Radiofrequency energy*, another invasive surgical measure, can be delivered to the sphincters with an anoscope and aims at treating FI. The number of treated patients is small. Artificial sphincter implantation or gracilis muscle transposition is only available in a few clinics internationally [23].

- **Stoma:** Only if other treatment modalities fail, a stoma should be considered: *Colostomy* is the final invasive option in FI's treatment. A stoma may improve QoL, and 80% of patients stated that they would choose to have it again [23].

Koloplastik: Stoma



SNS ... Sacral nerve stimulation;
PTNS ... Posterior tibial nerve stimulation

Figure 1-2: Management algorithm of faecal incontinence. Source:[23]

Nevertheless, these last invasive options in FI treatment have variable outcomes and can cause substantial comorbidity [11]. Bulking agents can be considered as a minimally invasive option in FI management [27].

Bulking Agents = minimal invasive Methode

1.3 Features of anal bulking agents

In 1993, polytetrafluoroethylene (Teflon or Polytef) injections were first reported to treat FI patients [10, 13]. Since then, numerous different bulking agents have been developed over the years [10]. Anal bulking agents, a minimally invasive surgical treatment, aim to prevent FI by increasing the pressure or closing the anal canal within the anal sphincter [1, 13, 16]. They are relatively easy to use and represent a minimally invasive intervention [1]. A further advantage is repeatability, i.e., replacement after removing protruding prostheses [27].

1993: Methode erstmals berichtet; Wirkprinzip: Verhinderung von FI durch Druckerhöhung im Analkanal, minimal-invasive Intervention

1.3.1 Comparator: Injectable anal bulking agents[10]

Injectable bulking agents are supposed to represent an alternative to conservative therapy options. Different substances with temporary durability are injected around the IAS. Hyaluronic acid (Non-Animal Stabilized Hyaluronic Acid (NASHA®), basis for dextranomer (Dx) microparticles), is injected and remains in the tissue. NASHA® Dx bulking agents are different from other bulking agents, apart from the substance used. They differ in the size of preparation, preventing migration into the surrounding tissue. NASHA® Dx was

injizierbare Bulking Agents:

Alternative zu konservativen Maßnahmen

Solesta®

[10] B0001 – What are implantable and injectable bulking agents?

launched under the brand name Solesta® (Salix Pharmaceuticals, Inc. Raleigh/ North Carolina) and is approved by the American Food and Drug Administration (FDA) [1].[11, 12]

Indikationen:

Zweitlinientherapie

Nowadays, a wide variation in types of materials used, surgical technique, and clinical indications are published [13]. The main clinical indication for injectable bulking agents is IAS disruption or dysfunction, causing passive FI [13]. In comparison to the EAS, the IAS is not amenable to surgical repair. Further clinical indications are:

Verletzung, Dysfunktion oder Schwäche des inneren Schließmuskels (IAS) Defekt des äußeren Schließmuskels (EAS)

- IAS damage (haemorrhoidectomy, anal stretch, delivery, sphincterotomy)
- Failure of conservative measures
- Structurally intact but weak IAS
- Defect in the EAS [13]

Surgical procedure and technique

Bulking agents' injections vary depending on the clinical indication and type of substance used. The bulking agent is placed submucosally within the IAS or the intersphincteric space and is injected using an anal retractor. It is recommended to use an endoanal ultrasound, guiding the needle to the optimum position [13].[13, 14]

1.3.2 Intervention: Implantable anal bulking agents[15]

implantierbare Bulking Agents: dünne Zylinder, die ihre Form und Größe unter Flüssigkeit verändern

Indikation: Zweitlinientherapie

Implantable bulking agents are thin cylinders that change their shape and size 48 hours after insertion, expecting to improve FI [1]. The implantable bulking agents can be seen as the latest generation of anal bulking agents, available as Gatekeeper™ and Sphinkeeper™ devices produced by THD s.p.A., Italy (originally from Medtronic, Minneapolis, USA) [1, 13]. Polyacrylonitrile (Hyexpan) is used, which is non-allergenic, inert, non-immunogenic, non-carcinogenic, and non-degradable [13]. Gatekeeper™ and Sphinkeeper™ are indicated for FI if conservative measures or injections of other bulking agents have failed [13].

Gatekeeper™ expandiert auf 500 mm³, jüngste Generation von Bulking Agents

Gatekeeper™: The dehydrated Gatekeeper™ prostheses consist of self-expandable, solid, thin cylinders (22 mm long, 2 mm diameter, 4-6 prostheses) [13, 14]. The material has hydrophilic properties: After implantation in the human tissue, the Hyexpan cylinders absorb water within 48 hours to become thicker and shorter (17 mm long, 6.5 mm diameter) [13]. Each implant's volume has an increase from approximately 70 mm^3 to 500 mm^3 and becomes softer in consistency [13]. The Gatekeeper™ procedure was modified to the Sphinkeeper™ procedure [12].

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11 A0020 – For which indications have implantable bulking agents received marketing authorisation or CE marking?

12 B0003 – What is the phase of development and implementation of implantable and injectable bulking agents?

13 B0004 – Who administers implantable and injectable bulking agents and in what context and level of care are they provided?

14 B0009 – What supplies are needed to use implantable and injectable bulking agents?

15 B0001 – What is the technology and the comparator(s)?

Sphinkeeper™: In comparison, the Sphinkeeper™ prostheses in a dehydrated state (29 mm long, 3 mm diameter, 10 protheses) change size within 48 h of contact with fluids (23 mm long, 7 mm diameter) [13]. The high number of implanted prostheses reach a final volume of implanted material; this is 8.650 mm^3 or approximately 480% increase in the size of the native sphincter [28].

Weiterentwicklung: Sphinkeeper™ expandiert um 480 %

Sphinkeeper™, titled the new artificial anal sphincter, can be seen as the evolution of Gatekeeper™, allowing treatments of more sizeable defects in the EAS or IAS [27, 28]. In 2019, the surgical technique Sphinkeeper™ was trialled for the first time at the Medical University of Vienna (MUW) [18].[16]

2019 erstmals an MUW erprobt

Implantation technique

The implantation technique of the Gatekeeper™ and Sphinkeeper™ is identical and performed under general or local anaesthesia, and intravenous antibiotics are prescribed. By the placement of an anal retractor, the IAS and intersphincteric groove can be identified. After an incision is made, the needle is positioned, and the prosthesis is released into the intersphincteric space. These steps may be repeated. Finally, the wounds are closed with a suture. This procedure is done as a day case and takes 30 to 40 minutes. Antibiotics and laxatives are prescribed to minimise the risk of adverse events and complications [13].[13]

wird unter Teilnarkose implantiert

zur Platzierung der Implantate wird ein Schnitt gemacht, genäht
Dauer: 30-40 Minuten

Implanting prostheses into the intersphincteric space of the anal canal shall avoid migration or extrusion. Due to their rapid increase in volume, the prostheses are not expected to move. Gatekeeper™ and Sphinkeeper™ are embedded within the intersphincteric space and push the IAS inwards and the EAS outwards. The sphincter contractility may be improved by the increased length of the sarcomere [13].[17] From a technical perspective, the procedure is relatively simple to perform, but issues with prostheses' placement and deployment can occur [11].

technisch einfach, aber Platzierung der Implantate und deren Migration ein Thema

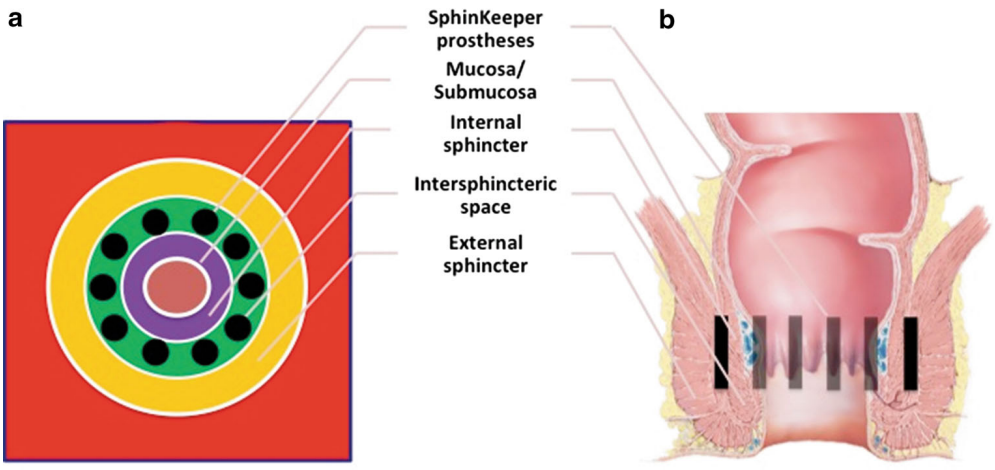

Figure 1-3: Site of implantation withing the interspincteric space. Source: [28]

[16] B0003 – What is the phase of development and implementation of implantable and injectable bulking agents?

[17] B0002 – What is the claimed benefit of implantable in relation to injectable bulking agents?

Whereas other anal bulking agents are injected around or into the anal canal, Gatekeeper™ and Sphinkeeper™ are implanted into the upper-middle inter-sphincteric space of the anal canal utilising a custom-made gun (Figure 1-3) [13, 14].

Current approval status of Gatekeeper™ and Sphinkeeper™

CE-Kennzeichen und zugelassen seit 2010

Both Gatekeeper™ and Sphinkeeper™ are approved in Europe and hold a CE marking (CE certificate Number HD60147418) [29], first registered in 2010 for the indication of FI [29].[18] Gatekeeper™ and Sphinkeeper™ have been registered in the following countries [29] (Table 1-1):

Table 1-1: Registration in other countries

Country	First certification	Description
EU	2010	THD Gatekeeper/THD Sphinkeeper
Australia	2010	THD Gatekeeper/THD Sphinkeeper
United Arab Emirates	2016	THD Gatekeeper/THD Sphinkeeper
Israel	2016	THD Gatekeeper/Sphinkeeper Family of Products
Serbia	2016	Registration Certificate_THD Gatekeeper/THD Sphinkeeper
Saudi Arabia	2017	Medical Device Marketing Authorization_THD Gatekeeper/THD Sphinkeeper
Malaysia	2018	Medical Device Registration Certificate_THD Gatekeeper/THD Sphinkeeper
Singapore	2019	Device Registration – THD Gatekeeper/THD Sphinkeeper
USA	-	Not approved
Canada	-	Not approved

in den USA und Kanada bislang nicht zugelassen

The FDA approved neither Gatekeeper™ nor Sphinkeeper™ for the U.S. market, and there is no approval trial ongoing. The same applies to Canada.

Estimated scope of services and expense

Annahme für Ö: bis zu 150 Leistungen p.a.

According to the submitting institutions' proposal, the annual estimated frequency in Austrian hospitals is 15 to 150 surgeries, i.e., three to 15 surgeries per hospital. The submitting hospitals mentioned no special premises or suppliers.[19, 20, 21] The cost of the prostheses is one-off, and routine controls are rare [13]. The submitting institutions did not provide information on the expanses of interventions.

keine Informationen zu Kosten vorliegend

Currently, neither injectable nor implantable bulking agents are included in the Austrian DRG system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF) [30].[22]

[18] A0020 – For which indications have implantable bulking agents received marketing authorisation or CE marking?

[19] A0011 – How much are implantable bulking agents utilised?

[20] B0008 – What kind of special premises are needed to use implantable and injectable bulking agents?

[21] B0009 – What supplies are needed to use implantable and injectable bulking agents?

[22] A0021 – What is the reimbursement status of implantable bulking agents?

2 Objectives and Scope

This update's scope is implantable bulking agents as a second-line therapeutic option in treating FI and their advantages compared to injectable bulking agents after conservative therapies failed. In contrast to the 2015 report, conservative treatments are not considered as comparators due to the indication of implantable bulking agents as second-line therapy [1, 13].

Update 2021: Einschränkung auf Zweitlinientherapie nach erfolgloser konservativer Therapie

2.1 PICO question

Are *implantable* bulking agents (Gatekeeper™, Sphinkeeper™) compared to *injectable* bulking agents in adult patients with faecal incontinence (if conservative measures fail) more effective and safe concerning FI severity, disease-related QoL, sustainability of effects, and procedure and device-related adverse events?

PIKO-Frage

2.2 Inclusion criteria

Inclusion criteria for relevant studies are summarised in Table 2-1.

Einschlusskriterien für relevante Studien

Table 2-1: Inclusion criteria

Population	Adult patients (≥18 yrs) with faecal incontinence in who conservative treatment interventions failed ICD-10 codes: Faecal incontinence (R15), Other specified diseases of anus and rectum (K62.8) MeSH term: fecal/faecal incontinence (D005242)
Intervention	Bulking agents – **implantations** (= products Gatekeeper™ and Sphinkeeper™) as second-line therapy
Control	Bulking agents – **injections**
Outcomes	
Efficacy	■ FI severity and incontinence episodes (Scores: Wexner Cleveland Clinic Faecal Incontinence Score (CCFIS), Vaizey score) ■ Disease-related QoL (Scores: Faecal Incontinence Quality of Life Scale (FIQL), American Medical Systems score (AMS)) ■ Sustainability of interventions: Durability of efficacy >6 months Rationale: Outcomes as assessed in the previous HTA 2015.
Safety	■ Procedure-related adverse events ■ Device-related adverse events
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series
Publication period	2015-2020
Languages	English, German

3 Methods

3.1 Research questions

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to this assessment's specific objectives [31].

Table 3-1: Health problem and Current use

Element ID	Research question
A0001	For which health conditions and for what purposes is the technology used?
A0002	What is faecal incontinence in the scope of this assessment?
A0003	What are the known risk factors for faecal incontinence?
A0005	What is the burden of disease for patients with faecal incontinence?
A0006	What are the consequences of faecal incontinence for society?
A0024	How is faecal incontinence currently diagnosed according to published guidelines and in practice?
A0025	How is faecal incontinence currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are implantable bulking agents utilised?

Table 3-2: Description of the technology

Description of the technology	
Element ID	**Research question**
B0001	What are implantable and injectable bulking agents?
A0020	For which indications have implantable bulking agents received marketing authorisation or CE marking?
B0002	What is the claimed benefit of implantable in relation to injectable bulking agents?
B0003	What is the phase of development and implementation of implantable and injectable bulking agents?
B0004	Who administers implantable and injectable bulking agents, and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use implantable and injectable bulking agents?
B0009	What supplies are needed to use implantable and injectable bulking agents?
A0021	What is the reimbursement status of implantable bulking agents?

Table 3-3: Clinical effectiveness

Element ID	Research question
D0005	How do implantable bulking agents affect symptoms and findings (FI severity, frequency) of faecal incontinence?
D0006	How do implantable bulking agents affect the progression (or recurrence) of faecal incontinence?
D0011	What is the effect of implantable bulking agents on patients' body functions?
D0016	How does the use of implantable bulking agents affect activities of daily living?
D0012	What is the effect of implantable bulking agents on generic health-related quality of life?
D0013	What is the effect of implantable bulking agents on disease-specific quality of life?

Table 3-4: Safety

Element ID	Research question
C0008	How safe are implantable in comparison to injectable bulking agents?
C0002	Are the harms related to dosage or frequency of applying implantable bulking agents?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of implantable bulking agents?
C0007	Are implantable and injectable bulking agents associated with user-dependent harms?

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted on the 17th of December 2020 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)
- HTA-INAHTA

The systematic search was limited to 2015 to 2020 and to articles published in English or German. Study designs for efficacy and safety were limited to RCTs, prospective non-randomised controlled trials, and prospective single-arm, before-after studies. After deduplication, overall, 158 citations were included. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov, WHO-ICTRP, EU ClinicalTrials [EUdraCT]) was conducted on the 14th of January 2021, resulting in 13 potential relevant hits.

insgesamt 159 Publikationen identifiziert

The manufacturer (THD s.p.A., Italy) of the assessed products (Gatekeeper™, Sphinkeeper™) submitted 15 publications, of which one was new; an accepted but still unpublished paper [32], resulting in overall 159 hits. By handsearch, no additional studies were found.

3.2.2 Flow chart of study selection

Literaturauswahl

Overall 159 hits were identified. The references were screened by two independent researchers (LG, CW), and in case of disagreement, a third researcher was involved in solving the differences. The selection process is displayed in Figure 3-1.

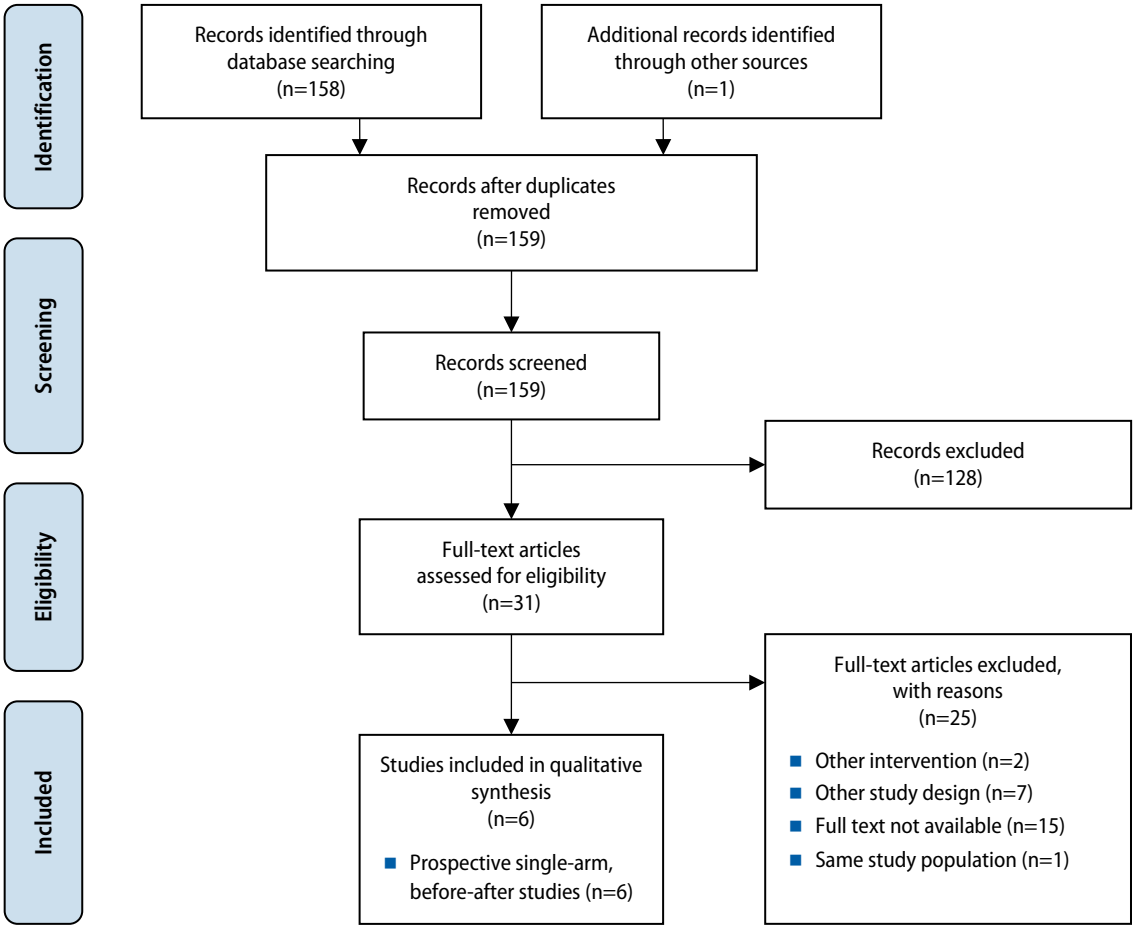

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Datenextraktion und Bewertung des Bias-Risikos laut IHE Checkliste

The data retrieved from the selected studies were systematically extracted into a data extraction table (see Appendix, Table A-2). No further data processing (e.g., indirect comparison) was applied.

Studies were systematically assessed for internal validity and risk of bias (RoB) by two independent researchers (LG, CW) using the Institute of Health Economics (IHE) RoB checklist for case series [33] presented in the Appendix (Table A-3). Overall, RoB was assessed using a predefined point score (range: 0-20, Table 3-5): Higher scores indicate a low RoB, and lower scores indicate a high RoB. Detailed thresholds are presented in Table 3-6.

Table 3-5: Overall risk of bias (RoB) point scores for RoB assessment of case series

Answers to specific questions of the IHE-20 checklist	Points
No	**0**
Partial	**0.5**
Unclear	**0.5**
Yes	**1**

Table 3-6: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of case series

Criteria	Points
Low risk	**> 18**
Moderate risk	**14.5 to 18**
High risk	**≤ 14**

3.2.4 Synthesis

Evidenzsynthese mittels GRADE

Based on the data extraction table (see Appendix, Table A-2), data on each selected outcome category were, if applicable, synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [34]. The research questions were answered in plain text format with reference to GRADE evidence tables (Table 5-1).

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

The following patient-reported outcomes – based on the systematic review 2015 [1] – were defined as most relevant to patients suffering from FI. Therefore, these outcomes are *crucial* to derive a recommendation:

- FI severity (measured by CCFIS or Vaizey Score)
- Disease-related quality of life (QoL) (measured by FIQL or AMS)
- Sustainability

FI severity was measured by two validated scoring systems [35-38]:

- **Wexner Cleveland Clinic Faecal Incontinence Score (CCFIS):** The CCFIS includes five parameters regarding the type of incontinence and five response options. The total score ranges from 0 (normal continence) to 20 (total incontinence). This score is used to assess FI severity and to document changes after FI treatment [37]. Clinical improvement denotes a minimum of 50% reduction in the scale score relative to the preoperative score [10] (Table 4-1).
- **Vaizey score** (St Mark's incontinence score): The Vaizey score, similar to the CCFIS, is used for severity assessment of FI and the evaluation of treatment outcomes. The total score ranges from 0 (perfect continence) to 24 (totally incontinent) [39] (Table 4-1).

Table 4-1: The Wexner Cleveland Clinic Faecal Incontinence Score (CCFIS) and Vaizey score; adapted from [36, 37, 39]

	Never	Rarely	Sometimes	Weekly	Daily
Incontinence for solid stool	0	1	2	3	4
Incontinence for liquid stool	0	1	2	3	4
Incontinence for gas	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4
Wears pad (only CCFIS item)	0	1	2	3	4
Need to wear a pad or plug (only Vaizey item)				No 0	Yes 2
Taking constipation medicines (only Vaizey item)				0	2
Lack of ability to defer defecation for 15 min (only Vaizey item)				0	4

Never = no episodes in the last month, Rarely = <1/month, Sometimes = <1/week, 1/month, Weekly = <1/day, ≥ 1/week, Daily = ≥ 1/day;

Add one more score from each row; minimum score 0 = perfect continence; maximum score 24 = totally incontinent

Disease-related QoL was measured by two validated scoring systems [35-38]:

- **Faecal Incontinence Quality of Life Scale (FIQL):** The FIQL comprises 29 items and forms four scales, including lifestyle, coping/behaviour, depression/self-perception, and embarrassment [38, 40]. The scale ranges from 1 (low status of QoL) to 5 (high status of QoL) [40] (see Appendix, Table A-1).

- **American Medical Systems score (AMS):** The AMS score is a modification of the FIQL and assesses the physical, psychological and social impact, pad use, lifestyle alterations, embarrassment/shame, depression, and coping/behaviour [38]. The AMS score is ranging from 0 (high status of QoL) to 120 (low status of QoL) [22]. By adding up the numbers, the status of QoL can be assessed (Table 4-2).

Table 4-2: The American Medical Systems score (AMS); adapted from [37]

Over the past four weeks, how often:	Never	Rarely	Sometimes	Weekly	Daily	Several times daily
Did you experience accidental bowel leakage of gas?	0	1	7	13	19	25
Did you experience minor bowel soiling of seepage?	0	31	37	43	49	55
Did you experience significant accidental bowel leakage of liquid stool?	0	61	73	85	97	109
Did you experience significant accidental bowel leakage of solid stool?	0	67	79	91	103	115
Has this accidental leakage affected your lifestyle?	0	1	2	3	4	5

Several times daily, >1 episode a day; daily, 1 episode a day; weekly, 1 or more episodes a week but <1 a day; sometimes, >1 episode in the past four weeks but <1 a week; rarely, 1 episode in the past four weeks; never, 0 episodes in the past four weeks. 0 = high status of QoL; 120 = low status of QoL

Sustainability of interventions

The sustainability of interventions is described with the durability of the potential improvement of FI severity and QoL, which was defined by >six months after surgery [1].

Further outcomes (per week or per month) were defined as *important*, but not crucial to derive a recommendation:

- Number of FI episodes
- Soiling
- Gas
- Liquid stool
- Solid stool

The number of FI episodes was not defined as crucial because patients' actual episodes reported and perceived do not always match. However, the number of FI episodes is a non-validated parameter [16].

Disease-specific mortality or mortality due to any causes were not considered to be relevant endpoints.[23]

[23] D0001 – What is the expected beneficial effect of implantable bulking agents on mortality?

4.1.2 Outcomes safety

The following outcomes were defined as *crucial* to derive a recommendation:

- **Procedure-related adverse events:** Intraoperative complications; postoperative complications and morbidity; infection, sepsis and inflammation; anal discomfort, pain and analgesia >48h; adverse effect, complication, and reaction
- **Device-related adverse events:** Dislodgement of prostheses and prosthesis removed or extruded

4.2 Included studies

4.2.1 Included studies effectiveness and safety

The systematic literature search (Figure 3-1) identified no comparative trials. Six prospective single-arm, before-after studies fulfilling the inclusion criteria for assessing clinical effectiveness and safety for implantable bulking agents, were included. Of those, five studies were single-centred [10, 16, 28, 32, 41], and one trial was conducted at multiple centres [22]. All studies, except one (Spain) [10], were conducted in Italy between 2011 [22] and 2018 [16, 32]. The sponsor was either not reported (4 studies), or it was declared that there was no commercial sponsor.

6 unkontrollierte, prospektive Vorher-Nachher-Studien mit 143 analysierten Pts: 81 Pts Gatekeeper™ (je 4-6 Implantate); 62 Pts Sphinkeeper™ (je 10 Implantate); nur 1 multi-centre Studie, 5 Studien in Italien durchgeführt

Within these six studies, a total of 149 patients were enrolled, 143 patients analysed. Losses to follow-up (FU) were reported in one study only (n=6) [32]. Eighty-one patients received Gatekeeper™ implants, and 62 patients received Sphinkeeper™ prostheses. The individual patients were treated with 4-6 Gatekeeper™ prostheses [10, 22, 41] or 10 Sphinkeeper™ prostheses [16, 28, 32].

The age of patients ranged from 20 [28] to 80 [22] years. Of the 143 analysed patients treated with implantable bulking agents, 112 were females. The assessed indications were passive FI [10, 41], passive, urge and mixed FI [28], and three trials did not specify the form of FI [16, 22, 32].

Alter: 20 bis 80 Jahre
112/143 Pts: Frauen

All studies, except two [16, 28], analysed short-term efficacy and sustainability for more than six months, i.e., durability of implantable bulking agents' effects. The number of patients per study at baseline ranged from seven [10] to 54 [22], and the FU period ranged from one [10, 22, 32, 41] to 36 [41] months.

4/6 Studien Nachbeobachtung >6 Monate

Study characteristics and results of included studies are displayed in the Appendix in Table A-2 and in the evidence profile in Table 5-1.

4.3 Results

keine vergleichenden Studien, daher auch kein Vergleich möglich

In the absence of data from controlled trials, no comparisons can be made between implantable and injectable bulking agents for FI's treatment. The *crucial* outcomes FI severity, disease-related QoL, sustainability, and procedure and device-related adverse events were considered when answering the research questions on how implantable bulking agents affect FI's symptoms and procedure-related risks.

The outcome FI severity was assessed in 143 patients, QoL in 84 patients, and safety in 143 patients. In the present review, FUs at three months and the last FUs (i.e., six, 12, 14, or 36 months) post surgery were compared.

Morbidity and Function[24, 25]

FI severity

Schweregrad mit CCFIS oder Vaizey gemessen

The crucial outcome of *FI severity* was assessed by the instruments CCFIS and/or the Vaizey Score.

CCFIS (alle 6 Studien): 5 Studien (133 Pts) berichten von stat. signifikanten Verbesserungen im Schweregrad zu unterschiedlichen Messzeitpunkten 1 Studie misst zwar, aber berichtet die Ergebnisse nicht

All six studies (143 patients) measured FI severity with the CCFIS preoperatively. In five studies [10, 16, 22, 32, 41] (133 patients) the CCFIS improved and one study [28] did not report postoperative data. FI severity significantly improved from baseline (mean ± SD) 12.4 ± 1.8 to 3-months FU 4.9 ± 1.5 ($p<0.0001$) and 36-months FU 4.4 ± 1.0 ($p<0.0001$; 20 patients) in one study [41]. In another study, CCFIS improved from preoperative (mean ± SD) 16.0 ± 4.0 to 3-months FU 10.4 ± 3.2 ($p<0.01$) and 12-months FU 10.1 ± 3.1 ($p<0.01$; 7 patients) [10]. Six months after operation, FI severity improved (mean (range)) to 8.91 (6.0–12.0; $p<0.05$) compared to baseline (12.46 (10.0–15.0); 13 patients) [16]. After 12 months postoperative, FI severity improved from (median (range)) preoperative 12.0 (3.0–20.0) to 5.0 (0.0–16.0; $p<0.001$; 54 patients) [22]. After 14 months, improvements from (median (1. and 3. quartiles)) 12.0 (9.0–15.0) to 7.0 (5.0–11.0; $p<0.01$) could be observed (39 patients) [32].

Vaizey (3 Studien): 2 Studien (93 Pts) s.s. Verbesserungen 1 Studie misst, aber berichtet nicht

The Vaizey score, also measuring FI severity, improved in two (93 patients) [22, 32] of three studies; one study did not report postoperative data [28]. FI severity improved from (median (range)) 14.0 (3.0–24.0) to 6.5 (0.0–17.0; $p<0.001$) at 12-months FU (54 patients) [22]. Furthermore, an improvement from (median (1. and 3. quartiles)) 15.0 (13.0–18.0) to 14-months FU 11.0 (7.0–14.0; $p<0.01$) was reported (39 patients) [32].

[24] D0005 – How do implantable bulking agents affect symptoms and findings (FI severity, frequency) of faecal incontinence?

[25] D0011 – What is the effect of implantable bulking agents on patients' body functions?

Sustainability of FI severity

Four studies (120 patients) [10, 22, 32, 41] reported on the sustainability of implantable bulking agents (i.e., durability of efficacy >6 months) in terms of FI severity.[26] Improvements in severity of FI, measured by the CCIFS, were reported after 12 ($p<0.01$ [10]; $p<0.001$ [22]), 14 ($p<0.01$ [32]), and 36 ($p<0.0001$ [41]) months postoperative. Two studies [22, 32] additionally measured FI severity by the Vaizey score. Severity of FI significantly improved after 12 ($p<0.001$ [22]) and 14 ($p<0.01$ [32]) months post surgery.

Nachhaltigkeit der Effekte >6 Monate in 4 Studien (120 Pts)

bleibende s.s. Verbesserungen nach 12, 14 und 36 Monaten

Disease-related quality of life[27]

The crucial outcome of *QoL* was assessed by the instruments FIQL and/or AMS.

FI-bezogene Lebensqualität mit FIQL und/oder AMS gemessen

Four studies measured QoL with the **FIQL** (84 patients) [10, 16 , 22, 28]. QoL, did not significantly improve in two studies (20 patients) [10, 16]; one study (10 patients) [28] did not report differences. Improved QoL could be found in one trial assessing lifestyle ($p<0.05$), coping/behaviour ($p<0.01$), depression/self-perception ($p<0.05$), and embarrassment ($p<0.01$) 12 months after surgery (54 patients) [22].

4 Studien (84 Pts): FIQL
1/4 Studien: s.s. Verbesserungen
2 Studien (64 Pts): AMS
1/2 Studien s.s. Verbesserungen

In two studies, the **AMS**, also measuring QoL, was additionally used in two studies (64 patients) [22, 28]. QoL significantly improved after 12 months from (median (range)) 87.0 (27.0–120.0) to 43.5 (0.0–106.0; $p<0.001$) [22]. The second trial did not report any postoperative data [28].

Sustainability of QoL

Two studies (61 patients) [10, 22] reported on the sustainability (i.e., durability of efficacy >6 months) of disease-related QoL. Significant improvements in QoL could be observed after 12 months measured by the FIQL (lifestyle and depression/self-perception $p<0.05$; coping/behaviour and embarrassment $p<0.01$) and the AMS score ($p<0.001$) [22]. The second trial found no statistically significant differences in QoL measured by the FIQL after 12 months post surgery [10].

Nachhaltigkeit der Effekte >6 Monate in 2 Studien (61 Pts)
1/2 Studien: s.s. Verbesserungen

Patient safety[28]

The crucial outcome of *safety* is divided into **procedure-related adverse events** and **device-related adverse events** to assess implantable bulking agents' safety. In total, 48 safety events occurred. A comparison between implantable and injectable bulking agents was not possible.

Sicherheit wird mit verfahrens- und produktbedingten Vorfällen beurteilt

Procedure-related adverse events

Intraoperative complications were reported in four (113 patients) [10, 16, 22, 32] of six studies and did not occur in three trials [10, 16, 32]. In three of 54 analysed patients, prostheses extruded during surgery [22]. Postoperative complications, morbidity, infection, sepsis and inflammation, were

intraoperative AE
postoperative AE
Schmerz im Analbereich
Komplikationen

[26] D0006 – How do implantable bulking agents affect progression (or recurrence) of faecal incontinence?

[27] D0013 – What is the effect of implantable bulking agents on disease-specific quality of life?

[28] C0008 – How safe are implantable bulking agents in comparison to injectable bulking agents?

reported in five studies [10, 16, 22, 28, 32] and did not occur in any of these trials. Anal discomfort, pain, and analgesia were reported in five studies [10, 16, 22, 28, 32]. Eleven of 123 analysed patients felt anal discomfort, pain or analgesia [10, 22, 28, 32]. Adverse effects, complications and reactions were reported in three studies [28, 32, 41], but did not occur in any patient.

Device-related adverse events

Dislokation von Implantaten in 31/143 Pts

Prostheses' dislodgement, i.e., migration/dislocation, was reported in all six studies and occurred in 31 of 143 analysed patients [10, 16, 22, 28, 32, 41]: Four (20%) [41], five (71%) [10], three (6%) [22], 18 (46%) [32], and one (8%) [16] patients. Prostheses had to be removed or extruded in three of 20 patients [10, 16], reported in three studies [10, 16, 28]. No evidence was available on user-induced harm and learning curves.[29]

No reliable information on subgroup analyses could be derived from the included studies.[30] Neither evidence on the effects on activities of daily living nor on generic health-related QoL was reported in the trials.[31, 32]

[29] C0007 – Are implantable and injectable bulking agents associated with user-dependent harms?

[30] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of implantable bulking agents?

[31] D0016 – How does the use of implantable bulking agents affect activities of daily living?

[32] D0012 – What is the effect of implantable bulking agents on generic health-related quality of life?

5 Quality of evidence

The IHE checklist assessed the RoB for the individual trials for single-arm studies, presented in Table A-3 in the Appendix [33]. Two researchers (LG, CW) independently rated the RoB. The overall RoB ranged from moderate to high, with three studies ranked as moderate [22, 32, 41] and three as high [10, 16, 28]. The main reasons for downgrading were the single-centre study designs, lack of patient characteristics, different patients' stage of disease when entering the study, and non-blinded outcome assessors.

The strength of evidence was rated according to GRADE schema [34] for each endpoint individually. Each study was rated by two independent researchers (LG, CW). All disagreements were resolved among the researchers. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [34].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

According to the GRADE scheme for the research question, the ranking can be found in the evidence profile below (Table 5-1).

The strength of evidence on the clinical effectiveness outcomes of implantable compared to injectable bulking agents could not be assessed due to the lack of controlled trials.

The strength of evidence for implantable bulking agents' safety outcomes is very low due to the study design, RoB and inconsistency in reporting safety outcomes.

Table 5-1: Evidence profile: Efficacy and safety of implantable bulking agents in patients with faecal incontinence

Quality assessment							Impact	Certainty (Importance)
Number of studies (Patients)	**Study design**	**Risk of bias33**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Efficacy								
Due to the lack of a controlled group, no data on efficacy outcomes can be compared and synthesised.								
Safety								
Procedure-related adverse events (FU: range 1 month to 36 months)								
6 (143 pts)	Observational, single-arm, before-after study	Very serious	Not serious	Not serious	Not serious	None	In 14 of 143 analysed pts ■ Intraoperative complications: n=3 ■ Postoperative complications/morbidity: n=0 ■ Infection/sepsis/inflammation: n=0 ■ Anal discomfort/pain, analgesia >48h: n=11 ■ Adverse effect/complication/reaction: n=0	⨁◯◯◯ VERY LOW (crucial)
Device-related adverse events (FU: range 1 month to 36 months)								
6 (143 pts)	Observational, single-arm, before-after study	Very serious	Not serious	Not serious	Not serious	None	In 34 of 143 analysed pts ■ Dislodgement of prostheses: n=31 ■ Prosthesis removed/extruded: n=3	⨁◯◯◯ VERY LOW (crucial)

Abbreviations: AMS – American Medical Systems score, CCFIS – Cleveland Clinic Faecal Incontinence score, FIQL – Faecal Incontinence, Quality of Life score, pts – patients, FU – follow-up

Nomenclature for GRADE table:
Limitations: 0: no limitations or no serious limitations; -1: serious limitations
Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency
Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty
Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

[33] Using the IHE RoB checklist, 3 studies with moderate and 3 studies with high RoB. Very serious limitations are given due to the lack of controlled trials.

6 Discussion

Faecal incontinence (FI), a common and highly prevalent condition (2-20% in the adult population), is the involuntary loss of intestinal contents [10-12]. Patients with FI suffer from a complex, stigmatising health problem causing physical and social impairments, negatively affecting the quality of life (QoL) and psychological wellbeing [1, 13-16]. After conservative measures fail, bulking agents can be seen as the final minimally invasive option in FI management [27].

Stuhlinkontinenz ist nicht nur medizinisches Problem, stigmatisierend und LQ beeinträchtigend

This update report 2021 aims to assess implantable bulking agents' clinical effectiveness and safety, a minimal invasive second-line therapy after failure of conservative interventions, compared to injectable bulking agents. The original report from 2015 dealt with *injectable* bulking agents compared to conservative therapies and (other) bulking agents, based on a Cochrane review dating from 2013. Since *implantable bulking agents* (Gatekeeper™ and Sphinkeeper™) are relatively new techniques, this report is – to our knowledge – the first systematic review, based on the best available evidence (prospective single-arm, before-after studies).

Ziel der Evidenzanalye: Wirksamkeit und Sicherheit von implantierbaren Bulking Agents im Vergl. zu injizierbaren Bulking Agents

The two implantable bulking agents (Gatekeeper™ and Sphinkeeper™) have been granted with the CE mark under the Medical Device Directive as early as 2010 (and a revision in 2020).

zugelassen in EU seit 2010

The majority of FI patients profit from conservative measures. In a review [42] with 574 FI patients, only nine per cent required surgical interventions. Thus, the importance of conservative measures in FI has to be highlighted.

Summary of evidence

The systematic literature search identified no comparative trials, but six prospective, before-after, single-arm studies as best available evidence with a total of 143 patients (median age range 20-80; 112 females) analysed (81 patients: Gatekeeper™; 62 patients: Sphinkeeper™). Of the six single-arm studies, five are conducted in Italy and one in Spain (single-centred: five; multi-centred: one). The individual patients were treated with four to six Gatekeeper™ prostheses or ten Sphinkeeper™ prostheses [1, 17, 32] each. The FU periods ranged between one and 36 months.

keine Vergleichsstudien, 6 prospektive Vorher-Nachher-Studien (143 Pts) je Pt 4-6 Gatekeeper™, 10 Sphinkeeper™-Prothesen implantiert

Clinical effectiveness and safety

The main findings are that the severity of FI (measured by the Cleveland Clinic Faecal Incontinence (CCFIS) or Vaizey Score) improved in the five studies that analysed pre and postoperative data [10, 16, 22, 32, 41] significantly. Unfortunately, neither for the CCFIS nor the Vaizey score thresholds were defined. It would be of interest, how many patients improved in FI [43]. Clinical relevant improvement of FI severity compared to baseline was denoted with a minimum of a 50% reduction in severity scales and number of FI episodes [10]. In this review, clinical relevant improvements in FI severity could be observed after three [10], six [16], 12 [10], and 14 [32] months. Regarding the number of FI episodes, the clinical relevant improvement could be shown in one study after three and 12 months [10]. The sustainability (i.e., durability of efficacy >six months) of the improvement in FI severity was observed in four studies after 12, 14, and 36 months post surgery [10, 22, 32, 41].

signifikante Verbesserungen im FI Schweregrad (5 Studien)

auch klinisch relevant

nachhaltige Effekte nach 12, 14 und 36 Monaten beobachtet

Verbesserungen in Lebensqualität (nur in 1 Studie)

Unfortunately, these improvements in FI severity did not show equal improvement in disease-related QoL (measured by FIQL and/or AMS): In only one of four studies, the QoL improved significantly [22]. This may be because i) the same (objective) FI severity might affect individual patients on a different level, and ii) the validation of the FIQL was only through translations.

Annahmen, dass Verbesserung im FI Schweregrad mit LQ korreliert

hier nicht gefunden

It is expected that FI has an impact on QoL as patients are unable to control stool or flatus, leading to embarrassment, fear of such FI episodes, and limitations in daily life and activities [40]. FI also affects psychosocial aspects [44]. QoL instruments are designed to measure the impact of FI on patients' life. Intuitively, the more severe FI is, the more an improvement will impact QoL: A correlation we assumed. However, QoL instruments should not be considered as a direct indicator of FI severity because the same (objective) severity level can affect different patients in a dissimilar way [45].

Übersetzung des engl. FIQL ins Italienische und Spanische als mögliche Ursache?

The FIQL, used in most included studies, has only been validated through translations (see Appendix, Table A-1). No subsequent English validation is published [44], and an Italian or Spanish validated version could not be found. This limitation includes issues with construct validity, reliability, and a complicated answering and scoring scheme [44]. Furthermore, cultural considerations about sexuality and religion have been a matter of concern [44]. These limitations may be reasons why QoL did not improve, even if FI severity did. Nonetheless, the FIQL has met psychometric criteria for validity and reliability and is recommended for assessing QoL in FI patients [40, 44].

Sicherheit: bei 22 % der Pts lösten sich 1 oder mehrere Prothesen von ihrer Platzierung

in retrospektiver Datenanalyse sogar 14-71 %

Safety aspects were reported in terms of procedure and device-related adverse events. Dislodgement of prostheses occurred in 22% of 143 analysed FI patients. Prosthetic displacement is a common adverse event with rates ranging between 14% and 71%, measured in a retrospective cohort-analysis using three-dimensional endoanal ultrasound [27]. The main cause of a possible progressive decline in a therapeutic effect are displacements of bulking agents [10]. Nonetheless, prosthetic displacements negatively correlate with postoperative changes in FI severity measured by CCFIS after 12 months [27]. Furthermore, implantable bulking agents can be replaced after removing protruded prostheses [27].

The National Institute for Health and Care Excellence (NICE) concluded that evidence on the safety and efficacy of self-expanding implant insertions into the intersphincteric space for FI is inadequate in quality and quantity; therefore, this procedure should only be used in the context of research [24, 46].

Gatekeeper™ vs Sphinkeeper™

matched Fall-Kontrollstudie (20 Pts):

Gatekeeper™ vs Sphinkeeper™ 6 vs 10 Prothesen ev. Vorteil von mehr Prothesen, insb. bei schwerer FI

A comparison between the two products was conducted in a small matched-control trial: Ten patients received ten Sphinkeeper™ prostheses each and were age-matched with ten patients having received six Gatekeeper™ prostheses each. The superiority of using a greater number of prostheses was shown in this comparative analysis [27]. Symptom severity measured by the CCFIS significantly improved in both groups after twelve months postoperatively. Though symptom improvement after Sphinkeeper™ implantation was 33% greater than with Gatekeeper™ implantation, it was not statistically significant. Muscle tension significantly increased in both groups compared to baseline but was significantly higher after Sphinkeeper™ implantation [27]. The

authors claim that a higher number and greater size of Sphinkeeper™ prostheses aim to enhance the bulking effect, resulting in better improvements in FI severity [27].

Furthermore, in a subgroup analysis (4 vs 6 prostheses in 20 patients), patients showed better results after implanting six prostheses [41]. These findings of two small studies suggest that more prostheses might be more effective [13]. Sphinkeeper™ might be indicated in patients with a more severe sphincter malfunction [47].[34]

Internal and external validity

Overall, the strength of evidence for clinical effectiveness outcomes was not assessed due to the lack of controlled trials. Regarding the safety of implantable bulking agents, the quality of evidence was very low.

Sicherheit: sehr niedrige Qualität der Evidenz

Several limitations of the best available evidence need to be taken into account: Across the six included prospective, single-arm studies, the overall risk of bias (RoB) was moderate (n=3) or high (n=3). Above all, the key limitation is that all included studies are highly prone to bias due to their uncontrolled before-after study design. Another major limitation is that all of the clinical outcomes were patient-reported. These subjective outcomes include a high risk of reporting bias, although the used questionnaires are validated. Further concerns were the studies' single-centred setup in five studies, lack of patient characteristics, different patients' stage of disease when entering the study, and non-blinded outcome assessors.

moderates (3 Studien) oder hohes (3 Studien) Verzerrungsrisiko:

unkontrolliertes Studiendesign, Pts-berichtete Endpunkte, Reporting Bias etc.

Concerning safety, procedure and device-related adverse events were counted on the number and percentages of patients. The small numbers of included participants across the studies (7-54 patients) could have influenced the occurrence of (serious) adverse events. In terms of external validity (see Appendix, Table A-4), data is considered generalizable to the Austrian context as the countries of recruitment were Italy and Spain. Treatments in the studies were performed in outpatient settings. In Austria, a day-case treatment is possible. But a hospital discharge is recommended after 24 h to avoid dislocations in the first hours.

kleine Studien: geringe Dokumentation von Nebenwirkungen und Komplikationen

bedingte Verallgemeinerbarkeit

Currently, four relevant ongoing studies examine bulking agents. Three observational studies with small numbers of patients; and one RCT compares anal bulking agents vs sacral nerve stimulation (see Appendix, Table A-5).

Limitations

No controlled trials were identified, and all studies included are prospective single-arm, before-after studies. Due to the lack of comparative studies, no information on the relative clinical effectiveness compared to injectable bulking agents can be given. On the other hand, retrospective studies were excluded, and possible safety data could have been missed. In the analyses of the six prospective studies, only procedure and device-related safety outcomes based on narrative descriptions – if documented at all – could be captured and analysed within the GRADE scheme.

keine kontrollierten Studien, daher keine Aussage zu vergleichenden klinischen Nutzen möglich

Ausschluss von retrospektiven Studien

[34] C0002 – Are the harms related to dosage or frequency of applying implantable bulking agents?

Buchkapitel in 2021: alle neuere Studien gesichtet – da Kontakt mit Hersteller

In 2021, a book section entitled 'Injectable and Implantable Biomaterials for Anal Incontinence' was published in the UK, not included in the present review. The authors report on safety and efficacy, which would be of further interest [48]. Since we contacted the manufacturer for additional unpublished data, no studies included in this book could be missed.

Berücksichtigung aller wesentlicher Endpunkte?

Verzögerung der Entleerung nicht berücksichtigt

The prespecified crucial outcomes for decision making (FI severity, QoL, sustainability, and safety) represent measures of the most important clinical therapeutic goals that were analysed in a standardised manner in all included studies. However, other patient-relevant outcomes, such as deferment of defaecation and subanalyses (e.g., the influence of obstetric trauma), were not subject to the present review; these outcomes were not relevant in the previous assessment dating back to 2015. FI is also defined as the inability to defer defaecation and evacuation to socially convenient times [41]. One year after Gatekeeper™ implantation, 80% of patients were able to defer defaecation for at least five minutes [22]. Some further publications report on improved deferment after Sphinkeeper™ surgeries: FI patients were able to defer evacuation for a minimum of five minutes [12, 49-51].

keine Subgruppenanalysen: etwa von Frauen nach Geburtstrauma

The principal aetiologic factor for FI in females is obstetric trauma [14]. Functional and/or structural abnormalities of the EAS and IAS are often secondary to traumatic vaginal delivery and, therefore, more common in women [14]. Many females had anal sphincter defects or lesion due to obstetric trauma or injuries at baseline (5/10 [27]; 9/15 [52]; 14/36 [53]; 13/14 [54]; 10/18 [11]). Unfortunately, no subgroup analyses were presented. However, implantable bulking agents have the potential to be effective in the presence of a history of obstetric anal sphincter injury [52].

Conclusion

relevantes Thema wegen demographischer Veränderung und individueller Betroffenheit

In the absence of comparative data, it is not possible to ascertain the relative benefit and risk of implantable compared to injectable bulking agents.

große Belastung der Betroffenen

Faecal incontinence (FI) is a highly relevant topic, not only due to demographic changes and obstetric traumas but also because of its stigmatising impact on an individual's wellbeing. It is crucial to understand patients' FI symptoms and severity to direct each patient to the most effective treatment pathway. Fortunately, the majority of FI patients profit from conservative measures and the importance of these treatments must be highlighted.

individuelle Therapielösungen

A precise assessment at presentation is essential to offer individual, tailored conservative therapy options. Implantable bulking agents might be a minimally invasive approach in FI treatment if conservative therapies fail. Implantable bulking agents are still early in their development, and clinical implementation is only considered as second-line therapy. In the analysed studies, the severity of FI improved significantly, but not so the quality of life. This discrepancy needs to be explored in further studies.

7 Recommendation

In Table 7-1, the scheme for recommendations is displayed, and the according choice is highlighted.

Table 7-1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

In the absence of comparative data, it is not possible to ascertain the relative benefit and risk of implantable compared to injectable bulking agents.

große psychische Belastung der Betroffenen

Faecal incontinence is a distressing condition that can substantially negatively affect individuals' quality of life. Thus, therapy options easing the severity of faecal incontinence may be justified, even in their early stages. The current evidence indicates that the assessed technology of implantable bulking agents (Gatekeeper™ and Sphinkeeper™) is still in an early stage of implementation (143 patients analysed in single-arm studies) but is promising to improve the severity of the disease and is relatively safe for treating faecal incontinence.

Technologie noch wenig erprobt

Empfehlung zugunsten restriktiver Einführung: in klinischen Studien, unter Dokumentation an spezialisierten Zentren

Despite the limited evidence of the included studies, i.e., no controlled studies, implantable bulking agents for faecal incontinence are recommended with restrictions to be conducted in clinical trials only and/or in specialised centres for selected patients. As a minimally invasive approach, bulking agents might be used only for faecal incontinence patients in whom conservative measures do not achieve sufficient effect.

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Appendix

Faecal Incontinence Quality of Life Scale (FIQL)

Table A-1: Faecal Incontinence Quality of Life Scale (FIQL)

Q1. In general, would you say your health is:		**Fair**	**Good**	**Very good**	**Excellent**
	5	4	3	2	1
Q2. Due to accidental bowel leakage:[35]	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**	**N/A**
a. I am afraid to go out	1	2	3	4	☐
b. I avoid visiting friends	1	2	3	4	☐
c. I avoid staying overnight away from home	1	2	3	4	☐
d. It is difficult for me to get out and do things like going to a movie or to church	1	2	3	4	☐
e. I cut down on how much I eat before I go out	1	2	3	4	☐
f. Whenever I am away from home, I try to stay near a restroom as much as possible	1	2	3	4	☐
g. It is important to plan my schedule (daily activities) around my bowel pattern	1	2	3	4	☐
h. I avoid travelling	1	2	3	4	☐
i. I worry about not being able to get to the toilet in time	1	2	3	4	☐
j. I feel I have no control over my bowels	1	2	3	4	☐
k. I can't hold my bowel movement long enough to get to the bathroom	1	2	3	4	☐
l. I leak stool without even knowing it	1	2	3	4	☐
m. I try to prevent bowel accidents by staying very near a bathroom	1	2	3	4	☐
Q3. Due to accidental bowel leakage:[36]	**Strongly agree**	**Somewhat agree**	**Somewhat disagree**	**Strongly disagree**	**N/A**
a. I feel ashamed	1	2	3	4	☐

[35] Please indicate how much of the time the issue is a concern for you due to accidental bowel leakage.
(If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, (N/A).)

[36] Please indicate the extent to which you AGREE or DISAGREE with each of the following items.
(If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, N/A).)

b. I can not do many of things I want to do	1	2	3	4	☐
c. I worry about bowel accidents	1	2	3	4	☐
d. I feel depressed	1	2	3	4	☐
e. I worry about others smelling stool on me	1	2	3	4	☐
f. I feel like I am not a healthy person	1	2	3	4	☐
g. I enjoy life less	1	2	3	4	☐
h. I have sex less often than I would like to	1	2	3	4	☐
i. I feel different from other people	1	2	3	4	☐
j. The possibility of bowel accidents is always on my mind	1	2	3	4	☐
k. I am afraid to have sex	1	2	3	4	☐
l. I avoid travelling by plane or train	1	2	3	4	☐
m. I avoid going out to eat	1	2	3	4	☐
n. Whenever I go someplace new, I specifically locate where the bathrooms are	1	2	3	4	☐
Q4. During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?					
1	Extremely So – To the point that I have just about given up				
2	Very Much So				
3	Quite a Bit				
4	Some – Enough to bother me				
5	A Little Bit				
6	Not At All				

Scale scoring:

Scales range from 1 to 5, with a 1 indicating a lower functional status of quality of life. Scale scores are the average (mean) response to all items in the scale (e.g., add the responses to all questions in a scale together and then divide by the number of items in the scale. Not Apply is coded as a missing value in the analysis for all questions.)

Scale 1. Lifestyle, ten items: Q2a Q2b Q2c Q2d Q2e Q2g Q2h Q3b Q31 Q3m

Scale 2. Coping/Behavior, nine items: Q2f Q2i Q2j Q2k Q2m Q3d Q3h Q3j Q3n

Scale 3. Depression/Self Perception, seven items: Q1 Q3d Q3f Q3g Q3i Q3k Q4, (Question 1 is reverse coded.)

Scale 4. Embarrassment, three items: Q21 Q3a Q3e

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-2: Gatekeeper™ and Sphinkeeper™: Results from observational studies

Product	Gatekeeper™			Sphinkeeper™		
Author, year	**Brusciano, 2020 [41]**	**De la Portilla, 2017 [10]**	**Ratto, 2016b [22]**	**Litta, 2021 [32]**	**La Torre, 2020 [16]**	**Ratto, 2016a [28]**
Country	Italy	Spain	Italy	Italy	Italy	Italy
Sponsor	None	NR	NR	None, (1 Col)	NR	NR (no Col)
Comparator	None	None	None	None	None	None
Study design	Prospective, before-after, single-arm, single-centre	Prospective, before-after, single-arm, single-centre	Prospective, before-after, single-arm, multi-centre	Prospective, before-after, single-arm, single-centre	Prospective, before-after, single-arm, single-centre	Prospective, before-after, single-arm, single-centre Feasibility study
Conducted in	01/2014-04/2016	NR	06/2011-11or 12/2013	03/2016-10/2018	12/2016-02/2018	07/2014-04/2015
Indication	Passive FI	Passive FI	FI not specified (passive, urge, or mixed)	FI not specified (passive, urge, or mixed)	FI not specified (passive, urge, or mixed)	FI Passive (n=4), urge (n=4), mixed (n=3)
Intervention	4 (n=4) or 6 (n=16) prostheses	6 prostheses	6 prostheses	10 prostheses	10 prostheses	10 prostheses
Number of pts at baseline	20 (20 females)	7 (6 females)	54 (37 females)[37]	45 pts	13 (10 females)	10 (5 females)
Number of pts analysed	20 females	7 (6 females)	54 (37 females)	39 (34 females)	13 (10 females)	10 (5 females)
Loss to FU, n (%)	0 (0)	0 (0)	0 (0)	3 (6.7) + 3 (6.7) excluded (unusable data)	0 (0)	0 (0)
Median age of patients, yrs median (range)	59 (24-77)	Mean age 55.6 (50.5-57.2)	66 (41-80)	68 (58-74)	NR (>18)	70 (20-75)
Inclusion criteria	FI onset ≥6 months; Symptoms being refractory to all standard conservative measures	Passive FI for mean duration of 6 ± 2 years; IAS lesion extending <60° of the anal circumference (mean 38 ± 4.0°)	18-80 years; FI onset ≥6 months; FI episodes >1x/week; Resistant to other conservative treatments; Intact anal sphincters or lesion only of IAS maximum circumferential extension of 60°	>18 yrs; FI onset ≥6 months; FI episodes >1x/week; Failure of conservative treatment; IAS and/or EAS defects <120°; Consent to the study; Attendance of all FU visits	>18 yrs; FI onset ≥6 months; FI episodes >1x/week; Resistant to conservative treatments; Intact anal sphincters or sphincter injury (IAS, EAS, or both); IAS and EAS defects	18-80 years; FI onset ≥6 months; FI episodes >1x/week; Willingness to perform FU

[37] Divided into two groups: Patients with ≥75% improvement in FI (group A; n=30) and patients with <75% improvement in FI (group B; n=24).

Product	Gatekeeper™			Sphinkeeper™		
Author, year	**Brusciano, 2020 [41]**	**De la Portilla, 2017 [10]**	**Ratto, 2016b [22]**	**Litta, 2021 [32]**	**La Torre, 2020 [16]**	**Ratto, 2016a [28]**
Exclusion criteria	IAS lesion >60° and/or EAS lesion >90°; Presence of active perianal sepsis; Severe anal scarring; Active treatments for anal or rectal cancer; IBD with anorectal involvement	NR	IAS lesion >60° or EAS lesion; Previous anal surgery for FI; Active perianal sepsis; Severe anal scarring; IBD with anorectal involvement; Anal or rectal cancer; Uncontrolled endocrine, metabolic or neurological disease; Congenital anorectal malformation	Diagnosis of cancer; IBD; Acute anorectal sepsis; Refractory chronic diarrhoea; Rectal bleeding; Sphincter defects >120°	Malignant neoplasms; Rectal bleeding; Congenital anorectal malformations; IBD; Sepsis; Obstructive defaecation syndrome; Neurological disease; Coagulation disorders	Malignancies under treatment; Rectal bleeding; Chronic diarrhoea; IBD; Acute anorectal sepsis; Concomitant rectal prolapse; Obstructive defaecation syndrome; Neurological disease; Coagulation disorder
Clinical outcome measures	Efficacy: FI severity (CCFIS) Safety: NR	Efficacy: FI severity (CCFIS (=Wexner), diary), QoL (FIQL) Safety: NR	Efficacy: FI severity (CCFIS, Vaizey, diary), QoL (AMS, FIQL) Safety: NR	Efficacy: FI severity (CCFIS, Vaizey) Safety: NR	Efficacy: FI severity (CCFIS, diary), QoL (FIQL) Safety: NR	Efficacy: FI severity (CCFIS, Vaizey, diary), QoL (AMS, FIQL) Safety: specified parameters
FU, months	1, 3, 6, 12, 24, 36	1, 3, 12	1, 3, 12 (FU median 12 ± 4)	1, 3, 6, annually (FU median 14 months (IQR, 7-23))	6	3
Outcomes						
Efficacy						
Incontinence episodes, severity and impacts						
CCFIS (mean ± SD [10, 41], median (range) [22, 28], median (1. and 3. quartiles) [32] or mean (range) [16])						
			Group A Pts with ≥75% improvement in FI (n=30)	Group B Pts with <75% improvement in FI (n=24)		
Preoperative	12.4 ± 1.8	16.0 ± 4.0	12 (3–20)		12 (9–15)	12.46 (10–15)	10 (5–17)
			13 (3–20)	9 (3–20)			
Postoperative 1 month	NR	10.7 ± 3.2; p<0.01	5 (0–17); p<0.001	7 (0–16); p=0.002	NR		
Postoperative 3 months	4.9 ± 1.5; p<0.0001	10.4 ± 3.2; p<0.01	4 (0–19); p<0.001	6 (0–16); p=0.002	NR		NR
Postoperative 6 months	NR				NR	8.91 (6–12); p<0.05	

Product	Gatekeeper™				Sphinkeeper™		
Author, year	**Brusciano, 2020 [41]**	**De la Portilla, 2017 [10]**	**Ratto, 2016b [22]**		**Litta, 2021 [32]**	**La Torre, 2020 [16]**	**Ratto, 2016a [28]**
Postoperative 12 months	NR	10.1 ± 3.1; p<0.01	5 (0-16); p<0.001		NR		
			4 (0–22); p<0.001	5 (1–16); p=0.002[38]			
Postoperative 14 months (median)					7 (5–11); p=0.001		
Postoperative 24 months	NR				NR		
Postoperative 36 months	4.9 ± 1.7; p<0.0001 (4.4 ± 1.0; p<0.0001 with 6 protheses)						
Vaizey (mean ± SD [10, 41], median (range) [22, 28], median (1. and 3. quartiles) [32] or mean (range) [16])							
Preoperative			14 (3-24)		15 (13–18)		13 (7–16)
			15 (3–24)	12 (5–21)			
Postoperative 1 month			5 (0–19); p<0.001	8.5 (0–18); p=0.012	NR		
Postoperative 3 months			4 (0–19); p<0.001	8.5 (0–18); p=0.012	NR		NR
Postoperative 6 months					NR		
Postoperative 12 months			6.5 (0-17); p<0.001		NR		
			4 (0–22); p<0.001	8 (2–17); p=0.012			
Postoperative 14 months					11 (7–14); p=0.001		
Nr of FI episodes (p.w. or p.m.)							
Preoperative		6.8 ± 2.6 p.m.	NR	NR		5.38 (2–11) p.w.	NR
Postoperative 1 month		3.0 ± 1.7 p.m.; p<0.05	NR	NR			
Postoperative 3 months		4.1 ± 2.0 p.m.; p<0.05	NR	NR			NR
Postoperative 6 months						1.57 (1–5) p.w; p<0.05	
Postoperative 12 months		5.1 ± 2.2 p.m.; p<0.05	NR	NR			
Postoperative 14 months							
Soiling (mean ± SD [10, 41], median (range) [22, 28], median (1. and 3. quartiles) [32] or mean (range) [16])							
Preoperative			>1x/day; n (%): 20 (37%)		7 (3–14)[39]		7 (2–49)
			4.0 (0–49)	2.5 (0–21)			

38 "24 patients (44 per cent) reported less than 75 per cent improvement in faecal incontinence parameters at 1-year follow-up."

39 Derivation of soiling outcome data is unclear, since soiling is not included in CCFIS or Vaizey and a diary is not mentioned in the methods section of the publication [32].

Product	Gatekeeper™				Sphinkeeper™		
Author, year	Brusciano, 2020 [41]	De la Portilla, 2017 [10]	Ratto, 2016b [22]		Litta, 2021 [32]	La Torre, 2020 [16]	Ratto, 2016a [28]
Postoperative 1 month			0.4 (0–22); p<0.001	1.5 (0–21); p=0.217	NR		
Postoperative 3 months			0.3 (0–20); p<0.001	0.8 (0–14); p=0.217	NR		NR
Postoperative 6 months					NR		
Postoperative 12 months			Never or <1x/week; n (%): 46 (85); p<0.001		NR		
			0.2 (0–21); p<0.001	0 (0–10); p=0.217			
Postoperative 14 months					3 (0–5); p=0.001		
Gas (mean ± SD [10, 41], median (range) [22, 28], median (1. and 3. quartiles) [32] or mean (range) [16])							
Preoperative			7.0 (0–49)	10 (0–40)	10 (4–14)		14 (0–35)
Postoperative 1 month			2.5 (0–49); p=0.015	2.5 (0–35); p=0.114	NR		
Postoperative 3 months			1.0 (0–49); p=0.015	5.5 (0–35); p=0.114	NR		NR
Postoperative 6 months					NR		
Postoperative 12 months			0 (0–49); p=0.015	0.1 (0–35); p=0.114	NR		
Postoperative 14 months					5 (2–14); p=0.002		
Liquid stool (mean ± SD [10, 41], median (range) [22, 28], median (1. and 3. quartiles) [32] or mean (range) [16])							
Preoperative			0.8 (0–49)	1 (0–20)	2 (1–5)		3 (0–21)
Postoperative 1 month			0 (0–3); p=0.003	0 (0–3); p=0.008	NR		
Postoperative 3 months			0 (0–4); p=0.003	0 (0–3); p=0.008	NR		NR
Postoperative 6 months					NR		
Postoperative 12 months			0 (0–21); p=0.003	0 (0–4); p=0.008	NR		
Postoperative 14 months					1 (0–2); p=0.002		
Solid stool (mean ± SD [10, 41], median (range) [22, 28], median (1. and 3. quartiles) [32] or mean (range) [16])							
Preoperative			0.5 (0–49)	0 (0–3)	1 (0–5)		0 (0–7)
Postoperative 1 month			0 (0–3); p=0.011	0 (0–0.5); p=0.015	NR		
Postoperative 3 months			0 (0–4); p=0.011	0 (0–1); p=0.015	NR		NR
Postoperative 6 months					NR		
Postoperative 12 months			0 (0–21); p=0.011	0 (0–7); p=0.015	NR		
Postoperative 14 months					1 (0–2); p=0.005		

Product	Gatekeeper™			Sphinkeeper™		
Author, year	**Brusciano, 2020 [41]**	**De la Portilla, 2017 [10]**	**Ratto, 2016b [22]**	**Litta, 2021 [32]**	**La Torre, 2020 [16]**	**Ratto, 2016a [28]**
Disease-related QoL						
FIQL: Lifestyle (mean ± SD [10], median (range) [22, 28] or mean (range) [16])						
Preoperative		NR	NR		2.62 (2.2–3.1)	3.2 (2.1–3.8)
Postoperative 1 month		NR; NS	NR			
Postoperative 3 months		NR; NS	NR			NR
Postoperative 6 months					3.2 (2.9–3.5); NS	
Postoperative 12 months		NR; NS	NR; p=0.01			
FIQL: Coping/behaviour (mean ± SD [10], median (range) [22, 28] or mean (range) [16])						
Preoperative		NR	NR		1.97 (1.7–2.2)	2.0 (1.2–2.9)
Postoperative 1 month		NR; NS	NR			
Postoperative 3 months		NR; NS	NR			NR
Postoperative 6 months					2.37 (2–2.6); NS	
Postoperative 12 months		NR; NS	NR; p=0.001			
FIQL: Depression/self-perception (mean ± SD [10], median (range) [22, 28] or mean (range) [16])						
Preoperative		NR	NR		2.96 (2.7–3.2)	3.6 (2.1–3.9)
Postoperative 1 month		NR; NS	NR			
Postoperative 3 months		NR; NS	NR			NR
Postoperative 6 months					3.39 (3.1–3.6); NS	
Postoperative 12 months		NR; NS	NR; p=0.029			
FIQL: Embarrassment (mean ± SD [10], median (range) [22, 28] or mean (range) [16])						
Preoperative		NR	NR		2.46 (2–2.8)	2.3 (2.0–4.0)
Postoperative 1 month		NR; NS	NR			
Postoperative 3 months		NR; NS	NR			NR
Postoperative 6 months					3 (2.7–3.4); NS	
Postoperative 12 months		NR; NS	NR; p=0.001			
AMS (median (range) [22, 28] or mean (range) [16])						
Preoperative			87 (27–120)			80 (26–114)
			94 (28–120)	82 (27–120)		
Postoperative 1 month			40.5 (0–94); p<0.001	64.5 (1–87); p<0.001		

Product	Gatekeeper™				Sphinkeeper™		
Author, year	Brusciano, 2020 [41]	De la Portilla, 2017 [10]	Ratto, 2016b [22]		Litta, 2021 [32]	La Torre, 2020 [16]	Ratto, 2016a [28]
Postoperative 3 months			32 (0–182); p<0.001	38 (0–80); p<0.001			NR
Postoperative 6 months							
Postoperative 12 months			43.5 (0–106); p<0.001[40]				
			32.5 (0–120); p<0.001	59 (1–105); p<0.001			
Outcomes							
Safety (n (%))							
Procedure-related adverse events							
Intraoperative complications	NR	0 (0)	3 (6) prostheses extruded during surgery		0 (0)	0 (0)	NR
Postoperative complications/morbidity	NR	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)
Infection/sepsis/ inflammation	NR	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)
Anal discomfort/pain, analgesia >48h	NR	1 (14.3) for 4 days	7 (13) for 4.4 (3.8) days		2 (5.1)	0 (0)	1 (10); for 1 week after surgery
Adverse effect/ complication/reaction	0 (0)	NR	NR		0 (0)	NR	0 (0)
Device-related adverse events							
Dislodgement of prostheses	4 (20)	5 (71.4) 24/42 protheses in 5/7 pts	3 (6)		18 (46.2)	1 (7.7)	0 (0)
Prosthesis removed/extruded	NR	1 (14.3)	NR		NR	2 (15.4)	0 (0)

Abbreviations: NR – not reported, UK – United Kingdom, n – number of patients, yrs – years, FI – feacal incontinence, IAS – internal anal sphincter, EAS – external anal sphincter, IBD – inflammatory bowel diseases, CCFIS – Cleveland Clinic Faecal Incontinence score, m – mean, SD – standard deviation, AMS – American Medical Systems score, QoL – quality of life, FIQL – Faecal Incontinence Quality of Life score, Wexner – Wexner scale assessment, NS – not significant, IQR – interquartile range, FU – follow-up, p.w. – per week, p.m. – per month

[40] Discrepancy could be observed as Group B had a range from 1-105 (not 106).

Risk of bias tables

Table A-3: Risk of bias – study level (case series), IHE checklist [33]

Study reference/ID	Brusciano, 2020 [41]	De la Portilla, 2017 [10]	Ratto, 2016b [22]	Litta, 2021 [32]	La Torre, 2020 [16]	Ratto, 2016a [28]
Study objective						
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Study design						
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	Yes	No	No	No
4. Were patients recruited consecutively?	Yes	Unclear	Yes	Yes	Yes	Yes
Study population						
5. Were the characteristics of the patients included in the study described?	No	No	Yes	Yes	No	Yes
6. Were the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Partial[41]	Yes	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Unclear[42]	No[43]	No[44]	No[45]	Unclear[46]	No[47]
Intervention and co-intervention						
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	No	No	Yes	Yes	Yes	Yes
Outcome measures						
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes	No
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes

[41] Only inclusion criteria stated.

[42] FI onset ≥6 months before the first visit.

[43] Patients were treated "after having suffered from passive FI for a mean duration of 6 ± 2 years".

[44] Duration of FI (years) 3 (1–19); mean (range)

[45] Duration of FI (years) 5 (2-10); median (first and third quartiles)

[46] "FI (incontinence to liquid and/or solid stools) that had started at least 6 months before."

[47] Median duration of FI (years; range) 9 (3–21)

Study reference/ID	Brusciano, 2020 [41]	De la Portilla, 2017 [10]	Ratto, 2016b [22]	Litta, 2021 [32]	La Torre, 2020 [16]	Ratto, 2016a [28]
Statistical Analysis						
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Unclear[48]	Yes	Yes	Yes	Unclear[48]
Results and Conclusions						
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	No[49]	No[50]
16. Were losses to follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes	Yes	Unclear[51]
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	No[52]	Unclear[48]
Competing interests and sources of support						
20. Were both competing interests and sources of support for the study reported?	Yes	No	Partial[53]	Yes[54]	No	Partial[55]
Points	**15.5**	**12**	**17.5**	**17**	**13.5**	**13**
Overall Risk of bias	**Moderate**	**High**	**Moderate**	**Moderate**	**High**	**High**

[48] No information given.

[49] Last FU 6 months after surgery.

[50] Last FU 3 months after surgery.

[51] No quantitative data provided.

[52] Significant results oft he FIQL (Table 2) were missing and in the conclusion is reported about “promising results”.

[53] Conflict of interest reported, but not sources of financial support.

[54] The last author “received travel reimbursement by THD company to attend conferences and was proctor in courses on SphinKeeper implant”.

[55] Source of financial support not provided.

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population enrolled in the studies is similar to the target population of the intervention in that FI patients are included (passive, urge, or mixed forms). All studies were conducted in a clinical routine with mainly female patients. In total, 149 patients were assessed, with 143 (112 females) analysed in the FUs. The range of age was between 24 and 80 years. The inclusion criteria of the included studies are in accordance with the intended patient population for the procedure. Bulking agents were applied as second-line therapy if conservative measures (first-line treatment) failed.
Intervention	Implantable bulking agents (Gatekeeper™, Sphinkeeper™) are the intervention at stake. All studies were conducted in clinical practice. Therefore, it can be assumed that the applied intervention corresponds to routine use. All studies applied implantable bulking agents as the intervention, using four to six Gatekeeper™ or ten Sphinkeeper™ prostheses. In the studies included in this assessment, both Gatekeeper™ and Sphinkeeper™ were used for second-line therapy for FI.
Comparators	To date, no studies are published comparing implantable and injectable bulking agents or vice versa. The comparator includes injectable bulking agents, also used as second-line therapy in patients suffering from FI. Injectable bulking agents represent an alternative to conservative therapy options.
Outcomes	Clinical effectiveness outcomes considered as crucial in this assessment were: FI severity measured by the CCFIS and Vaizey score and disease-related QoL assessed using the FIQL and AMS. All outcomes were patient-reported before and after surgery. Safety outcomes considered were procedure and device-related adverse events. FI severity was assessed in all six studies, and disease-related QoL was assessed in four of six trials. Most studies reported outcomes over three and twelve months. FUs ranged from one to 36 months, whereof three months preoperatively, and the last FU were considered for this report. The measured outcomes and timing reflect the most important clinical benefits and harms.
Setting	Five of the six included studies were conducted in an outpatient setting in Italy, and one study was conducted in Spain. The manufacturer, THD s.p.A., is located in Correggio, Italy. The studies reflect the settings in which the intervention is typically used.

Abbreviations: CCIFS – Cleveland Clinic Faecal Incontinence Score, FI – faecal incontinence, FU – follow-up, QoL – quality of life

List of ongoing trials

Table A-5: List of ongoing trials of bulking agents

Identifier/ Trial name	Study design	Number of patients (planned)	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT03080753	Single Group Assignment	52	Sphinkeeper	none	Severity of anal incontinence, postoperative infection, pain scores	December 2021	Region Skane (Sweden)
NCT04664868	Observational Prospective Study	11	Sphinkeeper	none	FI assessment, psychological/ physical wellbeing, migration of prostheses	November 2019	Medical University of Vienna (Austria)
ISRCTN00247992	RCT	50 vs 50	Anal bulking therapy	Sacral Nerve Stimulation	>50% reduction of the number of FI episodes	March 2015 Status completed, results overdue	Sahlgrenska University Hospital (Sweden)
ISRCTN61603070	Prospective trial	20	Sphinkeeper	none	Vaizey/ St Marks score, FIQL	January 2020	Poole Hospital (UK)

Literature search strategies

Search strategy for Cochrane

Search Name: Implantable Bulking Agents for Faecal Incontinence (MEL 2021)	
Last Saved: 17/12/2020 20:49:02	
Comment: LG/CW	
ID	Search
#1	MeSH descriptor: [Fecal Incontinence] explode all trees
#2	((faecal OR fecal OR anal OR bowel* OR gut* OR digesti* OR gastr*) NEAR (incontinen* or soil*)) (Word variations have been searched)
#3	MeSH descriptor: [Anal Canal] explode all trees
#4	("anal sphincter*") (Word variations have been searched)
#5	#1 OR #2 OR #3 OR #4 (Word variations have been searched)
#6	("bulking agent*") (Word variations have been searched)
#7	(Gatekeeper*) (Word variations have been searched)
#8	(Gate-keeper*) (Word variations have been searched)
#9	#6 OR #7 OR #8 (Word variations have been searched)
#10	#5 AND #9 (Word variations have been searched)
#11	(Sphinkeeper*) (Word variations have been searched)
#12	#10 OR #11 (Word variations have been searched)
#13	#12 with Publication Year from 2015 to 2020, in Trials (Word variations have been searched)
#14	#12 with Cochrane Library publication date Between Jan 2015 and Dec 2020 (Word variations have been searched)
#15	#13 OR #14 (Word variations have been searched)
Total hits: 31	

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily <1946 to December 15, 2020>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to December 15, 2020>	
Search date: 17.12.2020	
ID	Search
1	exp Fecal Incontinence/ (11499)
2	((faecal or fecal or anal or bowel* or gut* or digesti* or gastr*) adj3 (incontinen* or soil*)).mp. (17547)
3	exp Anal Canal/ (21113)
4	anal sphincter*.mp. (7317)
5	1 or 2 or 3 or 4 (36160)
6	bulking agent*.mp. (1664)
7	Gatekeeper*.mp. (7301)
8	Gate-keeper*.mp. (494)
9	6 or 7 or 8 (9426)
10	5 and 9 (166)
11	Sphinkeeper*.mp. (10)
12	10 or 11 (173)
13	limit 12 to yr="2015-2020" (85)
14	limit 13 to (english or german) (85)
15	remove duplicates from 14 (46)

Search strategy for CRD (DARE, NHS-EED, HTA)

Search Name: Implantable Bulking Agents for Faecal Incontinence (MEL 2021) LG/CW	
Search date: 17.12.2020	
ID	Search
1	MeSH DESCRIPTOR Fecal Incontinence EXPLODE ALL TREES
2	(faecal incontinen*)
3	(fecal incontinen*)
4	MeSH DESCRIPTOR Anal Canal EXPLODE ALL TREES
5	(anal sphincter*)
6	((faecal OR fecal OR anal OR bowel* OR gut* OR digesti* OR gastr*) NEAR (incontinen* or soil*))
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	(bulking agent*)
9	(Gate*)
10	#8 OR #9
11	#7 AND #10
12	(Sphinkeeper*)
13	#11 OR #12
14	(#13) FROM 2015 TO 2020
Total hits: 2	

Search strategy for Embase

Database Name: Embase.com		
Search date: 17.12.2020		
No.	Query Results	Results
#16.	#15 AND ([english]/lim OR [german]/lim)	134
#15.	#14 AND [2015-2020]/py	135
#14.	#12 OR #13	417
#13.	sphinkeeper*:ti,ab,kw,de,lnk,dn	17
#12.	#6 AND #11	405
#11.	#7 OR #8 OR #9 OR #10	107,383
#10.	'gate-keeper*':ti,ab,kw,de,lnk,dn	591
#9.	gatekeeper*:ti,ab,kw,de,lnk,dn	7,157
#8.	'bulking agent*'	2,639
#7.	'bulking agent'/exp	99,298
#6.	#1 OR #2 OR #3 OR #4 OR #5	34,481
#5.	(faecal OR fecal OR anal OR bowel* OR gut* OR digesti* OR gastr*) NEAR/3 (incontinen* OR soil* OR sphincter*)	23,625
#4.	'anus sphincter'/exp	9,281
#3.	'fecal incontinence'	8,228
#2.	'faecal incontinence'	3,704
#1.	'feces incontinence'/exp	21,619

Search strategy for HTA-INAHTA

Date of search: 17.12.2020	
Nr.	Search query,"Hits","Searched At"
12	(Sphinkeeper*) OR (((Gate-keeper*) OR (Gatekeeper*) OR ("bulking agent*")) AND (("anal sphincter*") OR ("Anal Canal"[mhe]) OR ((faecal OR fecal OR anal OR bowel* OR gut* OR digesti* OR gastr*) AND (incontinen* OR soil*)) OR ("Fecal Incontinence"[mhe]))),"1","2020-12-17T16:39:19.000000Z"
11	Sphinkeeper*,"0","2020-12-17T16:37:52.000000Z"
10	((Gate-keeper*) OR (Gatekeeper*) OR ("bulking agent*")) AND (("anal sphincter*") OR ("Anal Canal"[mhe]) OR ((faecal OR fecal OR anal OR bowel* OR gut* OR digesti* OR gastr*) AND (incontinen* OR soil*)) OR ("Fecal Incontinence"[mhe])),"1","2020-12-17T16:37:24.000000Z"
9	(Gate-keeper*) OR (Gatekeeper*) OR ("bulking agent*"),"13","2020-12-17T16:37:14.000000Z"
8	Gate-keeper*,"5","2020-12-17T16:36:50.000000Z"
7	Gatekeeper*,"6","2020-12-17T16:36:33.000000Z"
6	"bulking agent*","2","2020-12-17T16:36:11.000000Z"
5	("anal sphincter*") OR ("Anal Canal"[mhe]) OR ((faecal OR fecal OR anal OR bowel* OR gut* OR digesti* OR gastr*) AND (incontinen* OR soil*)) OR ("Fecal Incontinence"[mhe]),"67","2020-12-17T16:35:41.000000Z"
4	"anal sphincter*","19","2020-12-17T16:35:27.000000Z"
3	"Anal Canal"[mhe],"14","2020-12-17T16:35:03.000000Z"
2	(faecal OR fecal OR anal OR bowel* OR gut* OR digesti* OR gastr*) AND (incontinen* OR soil*),"57","2020-12-17T16:34:39.000000Z"
1	"Fecal Incontinence"[mhe],"21","2020-12-17T16:33:23.000000Z"
Total Hits: 0	Search query #12 limited to English/German

Search strategy for clinical trial registries

ClinicalTrials.gov (Expert Search Mode)
Date of Search: 14.01.2021

AREA[ConditionSearch] (Fecal Incontinence OR Faecal Incontinence OR Fecal Soiling OR Faecal Soiling OR Anal Incontinence OR Bowel Incontinence) AND AREA[InterventionSearch] (Bulking AND (sphincter OR implant OR implantable) OR Gatekeeper OR gate-keeper OR Sphinkeeper) AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[01/01/2015, 01/14/2021]

3 Studies identified

WHO ICTRP Basic Search Mode (Advanced Search not available on 14.01.2021)

Population: Fecal Incontinence, Faecal Incontinence, Anal Incontinence, Bowell Incontinence, Fecal Soiling, Faecal Soiling

Intervention: Bulking (agent), Gatekeeper, Gate-keeper, Sphinkeeper

NB: Each of the “Population” terms was manually entered and combined (with the Boolean “AND” Operator) with each of the above -also manually entered- “Intervention” terms. The (“Intervention”) term ‘sphinkeeper’ was additionally searched individually without Boolean combinations.

12 (**10** additional) studies identified

EU Clinical Trials [EudraCT] (Basic Search Mode)
Date of Search: 14.01.2021

Fecal Incontinence OR Faecal Incontinence OR Fecal Soiling OR Faecal Soiling OR Anal Incontinence OR Bowel Incontinence) AND (Bulking OR Gatekeeper OR gate-keeper OR Sphinkeeper)

Date range: 01.01.2015-14.01.2021

No studies identified

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