



Mid-term absorbable monofilament is safe and effective for gastrointestinal anastomosis – PROMEGAT - A single-arm prospective observational study

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ARTICLE INFO

Keywords:

Anastomotic leak
Gastrointestinal tract
Anastomosis
Monofilament suture

ABSTRACT

Introduction: Various suture materials and suture techniques are used to perform gastrointestinal anastomosis after tumour resection, but the best combination is still a matter of debate.

Methods: This multi-centre, international, single-arm, prospective observational study aimed at demonstrating the non-inferiority of a mid-term absorbable monofilament in comparison to braided sutures in gastrointestinal anastomosis. Monosyn suture was used to create the gastrointestinal anastomosis and the frequency of anastomotic leakage until day of discharge was chosen as the primary parameter. The outcome was compared to the results published for braided sutures in the literature. Secondary parameters were the time to perform the anastomosis, length of hospital stay, costs, and postoperative complications.

Results: The anastomosis leakage rate was 2.91%, indicating that Monosyn suture was not inferior to braided sutures used in gastrointestinal anastomosis. Of the reported anastomotic suture techniques, the single layer continuous method was the fastest and most economical technique in the present observational study.

Conclusion: Monosyn suture is safe and effective in gastrointestinal anastomosis and represents a good alternative to other sutures used for gastrointestinal anastomosis. With regard to safety, time and cost-efficiency, the single-layer continuous technique should be considered a preferred method. The transfer of results from clinical studies into daily practice with regard to surgical techniques for gastrointestinal anastomosis should be further evaluated in larger studies or in nationwide registries.

1. Introduction

To maintain the continuity of the gastrointestinal tract (GIT) after an intestinal resection, the construction of a gastrointestinal anastomosis (GIA) is a very important step. Gastrointestinal anastomoses have been performed for more than 150 years [1]. Due to a variety of different approaches, the best suture technique and ideal suture material for performing gastrointestinal anastomosis is still a matter of debate among surgeons. Currently, the single and double-layer technique are used and the suture material is applied using either the continuous or the interrupted suture technique [1–3].

Several studies and meta-analyses have compared the effectiveness of the single-layer versus the double-layer technique for GIA [1–9]. The most significant complication after a GIA is an anastomotic dehiscence at any level along the GIT, followed by a stricture or a sepsis developing due to the failure of the GIA. The results of several studies indicate that

the incidences of anastomotic dehiscence, perioperative complication rate and mortality are comparable between the two suture techniques [2,3]. However, the single-layer technique was superior in terms of time to perform the anastomosis [1–3,7,10,11] and was more cost-effective due to a shorter operation time and a lower amount of used suture material. Authors have concluded that the single-layer continuous technique is simple and easy to learn. The technique is reported to be as safe and effective as the double-layer technique or the single-layer interrupted technique [4,10–15]. Furthermore, the single-layer continuous technique has been evaluated as cheaper than stapling [1,3]. It has also been reported that patients receiving the single-layer continuous technique were able to tolerate oral fluids earlier than patients in whom the double-layer technique was used [3]. In addition, the risk of a stricture is lower with the single-layer continuous technique, most probably due to a reduction of ischemia and tissue necrosis compared to the double-layer technique [1]. Therefore, the single-layer

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continuous technique may be used routinely for GIA within the GIT [1–3].

The hypothesis of this prospective cohort study is that the monofilament mid-term absorbable suture (Monosyn[®]) used to create gastrointestinal anastomosis is not inferior to braided sutures, which were still in use during the planning phase of the PROMEGAT study, in terms of safety and efficacy.

2. Methods

2.1. Registration and ethics approval

In accordance with the declaration of Helsinki, this observational study was registered with www.clinicaltrials.gov under the registration number [NCT02080702]. The final study protocol has been approved by the ethics committees responsible for the participating clinics (Institutional Review Board of the Seoul National University Bundang Hospital, Institutional Review Board of the University of Malaya Medical Centre). Ethics approval was needed due to national requirements. A clinical study protocol was developed a priori but not published in a peer-reviewed journal.

2.2. Study design

The study was designed as an international, multi-centre, prospective, observational, single-arm study. Enrolment took place between February 2014 and March 2016 at two academic institutions and one community hospital. Of the participating clinics two were located in South Korea (Seoul National University Bundang Hospital, Department of Surgery, Seoul; Gyeonggi-do and GangNam Severance Hospital, Department of Surgery, Seoul) and one in Malaysia (University Malaya Medical Centre, Department of Surgery, Kuala Lumpur). Patients were monitored until day of discharge. The data collection and clarification was completed in May 2016.

2.3. Population and intervention

A population undergoing elective resection in the gastrointestinal tract due to a tumour disease (stomach, small intestine, colon) was recruited.

Patients were treated under routine clinical conditions and the surgical intervention as well as the suture technique used to perform the gastrointestinal anastomosis (GIA) were performed according to the clinic's standard or to the surgeon's preference.

Monofilament, mid-term absorbable suture (Monosyn[®] manufactured by B. Braun Surgical SA, Rubi, Spain) was applied in all the operations to create the GIA through the following potential suture techniques: single-layer continuous; single-layer interrupted; double-layer continuous inner and interrupted outer; double-layer continuous inner and outer; double-layer interrupted inner and outer. The suture material was applied by senior physicians, consultants and residents who had been trained in, and were familiar with, the use of a monofilament. Monosyn suture 2/0 and 3/0 in combination with a HR needle were used to create the GIA. A perioperative antibiotic prophylaxis was administered to all patients. Subgroup analysis of the anastomosis leakage rate according to the suture technique was performed.

2.4. Inclusion and exclusion criteria

Patients older than 18 years, scheduled for an elective resection in the gastrointestinal tract due to a tumour were eligible for this cohort study. All enrolled patients gave their written informed consent to the scientific analysis of their pseudonymized data set in accordance with the data protection law.

2.5. Exclusion criteria were

- ASA > 3
- Emergency operations
- Surgical interventions in the pancreas, oesophagus and rectum
- Patients with traumatic perforations
- Patients who had received chemotherapy within the last 4 weeks or radiotherapy on the treated region within the last 2 weeks
- Patients who were receiving immunosuppressant therapy.

2.6. Recruitment and follow-up

Patients were recruited from the patient population treated at the participating hospitals as part of daily clinical routine according to the clinic's standard. No additional follow-up visits were performed for this cohort study. On discharge from the hospital, the patient had completed the study.

2.7. Sample size calculation

The study was designed to prove the hypothesis of non-inferiority of a monofilament suture (Monosyn) to a braided suture for gastrointestinal anastomoses, which was still in use at the time point, when the PROMEGAT study was planned. A literature search performed on studies using either a braided or monofilament suture to create a gastrointestinal anastomosis was carried out in 2013. The summary of the studies [1,4–11,16–18] using a braided suture indicated an average anastomotic leakage rate of 8.3% compared to a leakage rate of 2.5% in monofilament sutures [1,6,8,10,12–15,19–31].

The non-inferiority hypothesis was considered proven, if the observed leakage rate for the Monosyn suture was significantly lower than the upper equivalence limit for braided sutures used for GIT. As the latter leakage rate averages 8.3% according to the summarized scientific literature, the upper equivalence limit for braided sutures is 11.3% with an equivalence margin of 3%. For sample size calculation, the expected anastomosis leakage rate in the study group was also set to 8.3%. Using this model, a sample size of 630 patients was calculated to show non-inferiority, using a one-sided binomial test with a significance level of 0.025 and a power of 80%.

2.8. Statistical methods

A one-sided binomial test was used to prove the non-inferiority of the Monosyn suture compared to the standard braided sutures in terms of the leakage rate.

The one-sided test significance level was set to 0.025.

With the inferiority hypothesis rejected, the nested hypothesis of a difference between the observed rate and the reported rate of 8.3% in braided sutures may also be proved without inflation of type 1 error. The analysis was performed using the SAS 9.4 software (SAS Inc., Cary, NC).

Subgroup-analysis of the anastomosis leakage rate according to the type of suture technique was performed.

2.9. Outcomes

An anastomotic leak is considered the standard outcome parameter for judging the efficacy of a GIA. Therefore, this parameter was chosen as the primary outcome and was compared to the results published for braided sutures in the literature. Occurrence of an anastomosis leak was confirmed by diagnostic measures (CT or MRI Scan) or by reoperation. In addition, the time to perform the anastomosis, the postoperative complication rate (peritonitis, wound infection, bleeding, abscess, fistula, perforation, obstipation, stenosis), costs and length of hospital stay were considered secondary outcomes.

This observational study was reported in accordance with the

STROCSS Guideline [32].

3. Results

3.1. Recruitment

Initially, the plan was to conduct this observational study as a multi-centre study in various hospitals located in Asia. Several hospitals were contacted in South Korea, Malaysia, Taiwan, Thailand, India, Indonesia, Philippines, Vietnam and Japan to ask if they wanted to participate. Unfortunately, a number of investigators contacted in Thailand, India, Indonesia, Vietnam, Japan showed no interest. Centres located in Taiwan and the Philippines were included but no patients were enrolled. In the end, recruitment was only performed at two centres in South Korea and at one centre in Malaysia. The first patient was recruited in February 2014. After the inclusion of 106 patients, the PROMEGAT study was prematurely terminated in March 2016 due to low patient recruitment. During the analysis, a violation of the inclusion criteria “tumour resection in the GIT” was discovered in three patients. As a result, these patients were excluded from the analysis. Therefore, a data set containing data on 103 patients was ultimately analysed. Due to the single-arm design of this observational study a flow chart is not provided and the demography and the intra-operative data will be reported descriptively.

3.2. Demography

In total 62 men and 41 women were enrolled. A mean BMI of $23.75 \pm 3.85 \text{ kg/m}^2$ was observed in the PROMEGAT study [range 16.18–36.92 kg/m^2]. The average age was 59.64 ± 10.82 years [range 38–85 years]. In total, 22.33% of the patients were current smokers and 33.01% consumed alcohol. In total 99 patients were Asian and 4 Caucasian. Most of the patients had an ASA II status (American Society of Anaesthesiologist Physical Status classification: ASA I = 38.83%, ASA II = 55.37% and ASA III = 6.80%). Diabetes was documented in 10 patients (9.71%) but no insulin dependent diabetes was recorded. Hypertension was observed in 33.98% of the patients.

3.3. Intra-operative data

Four patients underwent colorectal surgery, 49 resections were performed in the small intestine and 50 patients were treated due to a gastric disease. Most of the surgeries were performed by senior physicians (N = 50) or consultants (N = 50). Only 3 residents were reported as the responsible surgeon. A perioperative antibiotic prophylaxis was administered to all patients and intra-operative blood transfusion was required in 2 cases. A single anastomosis was created in each patient using Monosyn suture. The following types of anastomosis were recorded: ileo-ileal: N = 49; gastroenteric: N = 50; ileo-colic: N = 4. Various suture techniques were used to construct the anastomosis. The preferred suture technique was double-layer continuous inner and outer (47.57%), followed by single-layer continuous (28.16%), double-layer continuous inner and interrupted outer (20.39%). Four patients received the single-layer interrupted suture technique (3.88%). Regarding the USP size of the Monosyn suture used for anastomosis construction, in 99 cases 3/0 was chosen and 2/0 was chosen in 4 patients. All operations were performed with a round needle, predominantly HR26 mm. Depending on the suture technique 1–14 suture threads were required to perform the anastomosis. The preferred length of the thread was either 75 or 90 cm.

3.4. Outcomes

3.4.1. Primary outcome: anastomosis leakage rate

An anastomosis leak occurred in 3 patients up until the day of discharge (2.9%), 95% CI, [0.60–8.28%]. The extent of the insufficiency

regarding the circumference of the anastomosis was $\frac{1}{4}$ in one case and $\frac{1}{2}$ in another case. No details were reported in the third case. A CT scan was performed as a diagnostic measure. None of these patients stayed in the ICU. In one patient a reoperation was necessary and, in another case, a PCD clamping was performed. The therapeutic measures in the third case are not known.

The study hypothesis was to show the non-inferiority of Monosyn suture material compared to braided sutures. Using a binominal test, the confirmatory analysis showed a p-value of 0.002, which indicates that Monosyn is not-inferior to a braided suture for gastrointestinal anastomosis. The nested test to prove the difference revealed a one-sided p-value of 0.0245, which is still lower than the significance level of 0.025. This indicates that the leakage rate of Monosyn was potentially better than the reported leakage rates of braided sutures in the literature.

3.5. Secondary outcome: safety and efficacy parameter

A wound infection was observed in 2 patients (1.94%). The wound infections were classified as A1 superficial and diagnosed after 3 and 11 days postoperatively. In one case, a microbiological assessment was performed and *E. coli* was detected. In one case, an aseptic intervention was performed as a therapeutic measure and in the other case a limited aseptic intervention was performed. Peritonitis was diagnosed in one patient, pneumonia was recorded three times and the reoperation rate was 0.9%. No strictures, abscesses or ileus occurred.

Patients stayed in hospital for a mean duration of 7.97 ± 6.44 days after surgery. Two patients were transferred into the intensive care unit (ICU) after the operation. In another case, readmission to ICU was necessary due to a pneumonia and, after 44 days, the patient concerned died in the ICU.

Total operation times are shown in Table 1. A mean duration of 9.21 ± 9.68 min was recorded for the performance of the anastomosis [range 3–60 min]. The fastest suture technique was the single-layer continuous and the double-layer continuous outer and inner. The single-layer interrupted was the most time-consuming technique.

In terms of costs, the single-layer continuous and the double-layer continuous outer and inner were the most cost-efficient techniques based on the estimated procedural cost, because these were the fastest techniques and the techniques that consumed the least material. In contrast, the single-layer interrupted technique was the most expensive choice, with an anastomosis duration of 40–60 min and up to 14 thread applications required.

3.6. Subgroup analysis

Subgroup analysis of the anastomosis leakage rate according to the type of suture technique indicated 2 leaks in the double-layer continuous outer and inner out of 45 operations (4.4%). A third leak

Table 1
Secondary parameters.

	N	Min	Max	Median	Mean	StdDev
OP duration [min.]	103	80.00	436.00	210.00	220.56	74.85
Time for anastomosis [min.]	103	3.00	60.00	5.00	9.21	9.68
Time for anastomosis dependent on the technique [min.]	103					
DL continuous inner and interrupted outer	21	5.00	21.00	16.00	15.86	4.00
DL continuous inner and outer	49	5.00	8.00	5.00	5.35	0.60
Single layer continuous	29	3.00	12.00	5.00	5.31	1.56
Single layer interrupted	4	40.00	60.00	50.00	50.00	14.14
Length of hospital stay [days]	103	3.00	45.00	6.00	7.97	6.44

DL: double-layer.

occurred in one of three surgeries performed using the single-layer interrupted suture technique (33.3%). No anastomotic leak was diagnosed in either the single-layer continuous suture technique (N = 29) or in the double-layer continuous inner and interrupted outer technique (N = 17). The single-layer interrupted suture technique was only used at the hospital in Malaysia to perform ileo-colic anastomosis. In the centres in South Korea, ileo-ileal anastomoses were constructed using either the single-layer continuous technique (N = 28) or the double-layer continuous inner and interrupted outer technique (N = 21), whereas for gastroenteric anastomosis the double-layer continuous inner and outer was used in most cases (N = 49). One patient received the single-layer continuous suture technique for this type of anastomosis. In South Korea, senior physicians performed the gastroenteric anastomoses, whereas all ileo-ileal anastomoses were constructed by consultants. In Malaysia, 3 surgeries were performed with a resident as the leading surgeon and one with a consultant as the leading surgeon.

4. Discussion

Anastomotic leak within the GIT is associated with high morbidity and mortality. The clinical outcome of an anastomosis in the GIT depends on adequate tissue layer apposition, a good blood supply, a tension-free approximation and the height of the anastomosis. The leakage rate is the common parameter for judging the effectiveness of the anastomosis. The overall reported leakage rate in the literature is between 0 and 18% [1,4–7,33–37]. Therefore, measures for decreasing postoperative leaks and leakage-associated complications are of great interest.

Numerous clinical studies and meta-analysis have been performed analysing different suture materials (monofilament vs. braided) or different suture techniques (single-layer vs. double-layer) for GIT anastomosis to generate clinical evidence. Currently, no clinical investigation has shown the superiority of the single-layer technique compared to the double-layer technique for GIT anastomosis. The suture technique used and suture material depends on teaching and on the preference of the individual surgeon.

The double-layer technique (DL) is technically more challenging and requires the identification of individual layers. Each layer has to be separately approximated, leading to the risk of suture tension and ischemia. In addition, the circumference of the intestinal lumen is reduced due to the multi-layer closure. In comparison to the single-layer suture technique, DL is, in general, more time-consuming and entails the implantation of a higher amount of foreign material. Using the single-layer suture technique entails a higher risk of dehiscence because only the outer layer of the bowel is included, or of narrowing the intestinal lumen when the full thickness technique is used. A lower rate of tissue necrosis and a reduction of ischemia have been observed. The last meta-analysis published by Sajid et al., in 2012 showed equivalence with regard to the leakage rate, the incidence of postoperative complications and mortality. In this meta-analysis, the length of hospital stay was comparable and use of the single-layer suture technique led to a shorter operation time. Sajid and Shikata recommended the routine use of the single-layer technique because of the shorter operation duration and being more economical with a comparable safety outcome compared to the double-layer suture technique [2,3]. The limitation of both meta-analyses is that the outcome is based on small patient numbers and on moderately designed studies. The recent RCT by Herrle et al. [33] published in 2016 on colorectal anastomosis could not draw any definitive conclusions with regard to whether the two suture techniques are comparable or if one technique is superior due to the premature termination of the study.

The aim of this study was to assess the performance of monofilament suture used for gastrointestinal anastomosis as part of daily routine using the suture technique preferred by the surgeon or the clinic's standard. We hypothesise that the Monosyn monofilament suture is equivalent to a braided suture. In our observational study, the majority

of interventions were gastro-enteric and ileo-ileal anastomoses.

The anastomosis leakage rate of 2.9% detected with Monosyn was well within the range of the anastomosis leakage rates reported for other monofilament sutures (mean rate = 2.5%) [1,6,8,10,12–15,19–31] and even superior to published rate for braided sutures (mean rate = 8.3%) [1,4–11,16–18]. This significant difference proved the study hypothesis, despite the fact that the number of patients recruited (N = 103) was considerably lower than planned (N = 630).

Depending on the suture technique, anastomotic leak incidence ranges from 1.2 to 3.1% for the single-layer continuous technique and 1.5–12% for the double-layer technique [1,33–36]. Our subgroup analysis showed no leak in the single-layer continuous group and an incidence of 4.4% in the double-layer continuous group. Hence, there was no obvious difference compared to the literature. Regarding wound infections, we observed two cases with SSI (1.9%), which is comparable to data reported by Reggio et al. [34] but much lower than the rates published by Herrle et al. which are mainly determined by the inclusion of only colorectal anastomosis [33]. We observed no strictures or abscesses and the incidence of peritonitis was 0.97%. The mean duration of the hospital stay was 7.97 days in our population. This is almost equal to the mean duration of the stay in the Burch study [1], the Herrle study [33] and the Reggio study [34].

Burch et al. mentioned that single-layer anastomosis can be performed by an experienced surgeon in 8–10 min [1]. In contrast, it is difficult for an experienced surgeon to create a double-layer anastomosis in less than 20–25 min. In our study, a mean time of 9.21 min was needed to create the anastomosis irrespective of the suture technique used.

Depending on the type of suture technique the mean duration required to construct a single-layer continuous anastomosis was 5.31 min and 15.85 min for the double-layer continuous inner and interrupted outer. Therefore, less time was required for single-layer continuous anastomoses and the time saving was well within the range reported by other authors [1,3,33,34,36,37]. The most time consuming technique was the single-layer interrupted suture technique, which was performed in only 4 cases with a mean duration of 50 min.

The single-layer continuous suture technique was found to be the most cost-effective method because of lower material consumption and significantly shorter construction time compared to the double-layer anastomosis [1,3,36,37]. This was supported by the results of the current study. In addition, from an economic and a safety perspective, the single-layer interrupted anastomosis should be considered very carefully against the other methods as it had the highest leakage rate (33%), the longest construction duration and required the highest material investment (10–14 threads) of all the techniques studied in this study. Furthermore, the difference in cost is more dramatic for single-layer continuous surgical techniques if compared with stapled anastomosis, which requires the use of a disposable gun and some refills. With a safety outcome comparable to that of using an optimized hand-sewn anastomosis, the pros and cons of using stapling devices should be carefully evaluated in today's cost-conscious healthcare environment. In summary, our findings are consistent with those available in the literature.

This study has limitations, such as the use of a historical control group and a short term postoperative follow-up. A further weakness is the small sample size and the limited inclusion of colonic anastomosis and the exclusion of oesophageal, pancreatic and rectal anastomosis, which have a higher risk of postoperative leakage. As in the study published by Herrle et al. [33], this cohort study was also prematurely terminated due to slow recruitment at the participating centres and low interest among the other clinics contacted. Besides adequate infrastructure at the study centres and appropriate funding per recruited case, interest in scientific questions regarding routine daily procedures is an essential success factor for future multi-centre surgical studies including a huge patient enrolment. In the future, large patient

observational studies or nationwide registries should be started for interventions performed in daily practice to clarify surgical research questions. This is also supported by Slieker et al. who concluded that routine detailed documentation of anastomotic technique of all colorectal operations will be instrumental in formulating a definitive conclusion on the role of the unstandardized hand-sewn colorectal anastomosis [38].

In conclusion, this single arm, multi-centre, international, prospective observational study has shown that the mid-term absorbable monofilament suture Monosyn can be considered as safe and as efficient as a braided suture in gastrointestinal anastomosis performed as part of clinical practice. Considering safety, time, material and costs, the single-layer continuous suture technique should be considered as the procedure of choice for the majority of gastrointestinal anastomosis in daily routine.

Ethical approval

Study was approved the ethics committees responsible for the participating clinics.

Positive ethics approval was obtained by the Institutional Review Board of the Seoul National University Bundang Hospital and by the Institutional Review Board of the University of Malaya. E-1312/230-002.

Sources of funding

This cohort study was sponsored and funded by Aesculap AG.

The sponsor was responsible for project management, data management, statistics and for study registration. Sponsor was involved in the preparation of the manuscript, in the decision of journal selection and in the submission process of the manuscript.

Author contribution

Petra Baumann and Moritz Wente designed the study. Jongwon Kim, Sang-Hoon Ahn, Hyung-Ho Kim and Hoong-Yin Chong performed the data collection. Viktor Breul (contributor) was responsible for data analysis. Petra Baumann and Moritz Wente wrote the manuscript. Manuscript was reviewed and approved by Jongwon Kim, Sang-Hoon Ahn, Hyung-Ho Kim and Hoong-Yin Chong.

Conflicts of interest

Petra Baumann and Moritz Wente are employees of Aesculap AG.

Dr. Jongwon Kim, Sang-Hoon Ahn Dr. Hyung-Ho Kim and Hoong-Yin Chong declare no conflict of interest.

Consent

The authors declare that written informed consent has been obtained by all enrolled patients according to data protection law.

Research registration number

Study was registered on the 5th March 2014 at www.clinicaltrials.gov under the registration number [NCT02080702].

Guarantor

Petra Baumann and Moritz Wente are guarantors for this cohort study.

Acknowledgements

The authors thank all the surgeons and all the patients at the

participating centres who participated in this cohort study (GangNam Severance Hospital, Department of Surgery, Seoul, South Korea; Seoul National University Bundang Hospital, Department of Surgery, Gyeonggi-do, South Korea; University Malaya Medical Centre, Department of Surgery, Kuala Lumpur, Malaysia). Special acknowledgment is due to Viktor Breul (Aesculap AG) who performed the statistical analysis.

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