Gentamicin submucosal lavage during peroral endoscopic myotomy (POEM): a retrospective analysis

Julia Bayer¹² • Zuzana Vackova¹ • Hana Svecova³ • Petr Stirand¹ • Julius Spicak¹ • Jan Martinek¹⁴⁵

Abstract

Background and aims Peroral endoscopic myotomy (POEM) is an evolving therapeutic modality for achalasia. According to the original Inoue’s technique, a submucosal lavage with gentamicin has been practiced due to the fear of infection. This single-tertiary center study was intended to assess the clinical significance of the topical antibiotic lavage during POEM.

Methods A retrospective analysis of prospectively collected data was conducted. The outcomes of patients who received the gentamicin lavage (group A) during POEM were compared to those who did not (group B). The main outcome variables were infectious adverse events, post-POEM fever, and markers of systemic inflammatory response. One day before and after POEM, all patients received systemic antibiotic prophylaxis with ceftriaxone.

Results Of 124 consecutive patients having undergone POEM, 60 patients received a lavage with 80 mg of gentamicin into the submucosal tunnel before starting the myotomy, while 64 patients did not. The overall treatment success at 3 months did not differ between the two groups (group A 94.7 vs. 97.5% group B). We did not experience any significant infectious adverse events in either group. CRP and WBC levels were lower in patients with lavage versus those without [CRP: median 52.7 (IQR 34.9) vs. 69.5 (54.1); p = 0.01; WBCs: median 10.9 (IQR 3.3) vs. 12.6 (3.9); p < 0.01]. Post-procedural fever was present in 10% of patients in either group.

Conclusions During POEM, the submucosal lavage with gentamicin prior to the myotomy does not play a role in the prevention of clinically significant infectious adverse events, although the systemic inflammatory response may be decreased.

Keywords Per-oral endoscopic myotomy • Gentamicin submucosal lavage • Achalasia • Infectious adverse events

Achalasia is an esophageal motility disorder characterized by the loss of the myenteric nerve plexus leading to disturbed peristalsis and impaired relaxation of the lower esophageal sphincter (LES). A causal treatment is not available; all treatments are aimed to decrease the tonus of a hypertensive LES and thus improving symptoms such as dysphagia and regurgitation. Traditionally, patients with achalasia have been offered botulinum toxin injection, balloon dilatation, or laparoscopic Heller myotomy (LHM). All these treatments are effective (with LHM being considered as the most effective treatment with a long-term perspective) and safe [1–3]. Peroral endoscopic myotomy (POEM) is a novel therapeutic modality for patients with achalasia. It is a scarless procedure where a myotomy is performed endoscopically using a principle of submucosal tunneling [4]. Compared to LHM, it may have several

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advantages (possibility of performing longer myotomy in patients with spastic motility disorders, no scars, possibly lower invasiveness, usage after failure of LHM) and some disadvantages (e.g., post-POEM reflux may be more frequent than after LHM). However, final answers will be available after completion of the randomized study comparing LHM with POEM, which is currently underway.

Several studies have demonstrated excellent short-term efficacy and safety of POEM [5–7]. Surprisingly, infectious adverse events after POEM are extremely rare even though the procedure is performed with a non-sterile endoscope which is located in the mediastinum. Besides administration of systemic antibiotics, a submucosal lavage with gentamicin (performed after completing the myotomy) was used in the original description of Inoue’s technique [4, 8]. Because of pain with the latter, the lavage was instead performed before starting the myotomy. The absence of infectious adverse events has lead several centers, including our own, to abandon the lavage. There are no data, however, assessing the role of the gentamicin submucosal lavage. The aim of this analysis is to assess the clinical role of the submucosal gentamicin lavage in patients undergoing POEM. We retrospectively compared outcomes of patients with and without the lavage, and the main outcome measurements were infectious adverse events and markers of systemic inflammatory response.

Materials and methods

Patients

We retrospectively analyzed prospectively collected data of consecutive patients who underwent POEM in our center since December 2012 until March 2016. A total of 124 patients underwent POEM all of which met diagnostic criteria for achalasia based on high-resolution manometry (HRM), barium swallow, and endoscopy. All patients treated from 2012 to March 2014 received the gentamicin lavage, between March and October 2014 still most did, and all subsequent patients did not. Overall, 60 patients received the lavage while 64 did not.

POEM technique and peri- and post-procedural protocol

POEM procedures were performed with the approval of a Local Ethical Committee and the patients signed an informed consent form as POEM was not considered a standard procedure in 2012–2014. POEM was performed according to the original Inoue’s technique [4, 5] which consists of the following steps: submucosal injection of saline, mucosal incision, creation of submucosal tunnel, esophageal myotomy, and closure of mucosal entry site with endoscopic clips. For all POEMs, we used a high-resolution endoscope Olympus 180 or 190 (Olympus Medical Systems, Tokyo, Japan), and myotomy was performed with a triangle knife (Olympus Medical Systems, Tokyo, Japan). We used Erbe 300D electrosurgical unit (ERBE, Tübingen, Germany) with the electrosurgical settings as follows: incision—Endocut I, effect 1, duration 1, interval 3; tunneling and myotomy—spray coagulation, effect 2, and watts 50.

The majority of patients underwent POEM at 2 o’clock, and five patients had POEM on the posterior wall at 5–6 o’clock (re-POEM or POEM post-LHM). We performed a full-thickness myotomy to increase efficacy; in fact, the longitudinal esophageal layer often easily disrupts itself after the circular muscle is myotomized.

When we started our POEM program in 2012, patients were hospitalized until postoperative day (POD) 2 to assure the absence of adverse events. Later, we started discharging the patients on POD 1, whenever it was possible.

Within 1 h before the procedure, all patients were given i.v. ceftriaxone 2 g and metronidazole 500 mg; ceftriaxone was further administered on POD 1. Anti-fungal prophylaxis has not been used routinely and only patients with mycotic esophagitis received fluconazole orally 1 week before POEM and i.v. 1 h before the procedure.

Blood for analysis of C-reactive protein (CRP), white blood cell (WBC) count, and other parameters including serum creatinine was drawn in all patients one day before POEM and on POD 1. On POD 1, barium swallow was performed to exclude a leak through the closed incision. In patients with such a leak, upper endoscopy was performed to check the entry point and, if necessary, clips were added. Then the patients received a liquid diet, and analgesics were given on a demand basis. Body temperature was measured before and three times daily after POEM until discharge on POD 1 or 2. All patients have been followed up at 3, 6, 12, 24, and 36 months to check for clinical efficacy and adverse events (e.g., reflux esophagitis).

Gentamicin lavage

In 60 patients (48.4%), a lavage with 80 mg of gentamicin diluted in 10 mL of normal saline was performed into the submucosal tunnel before starting the myotomy (= group A). In 64 patients (51.6%), the gentamicin lavage was not performed (= group B).

Statistical analysis

The aim of this study was to compare pre-defined outcomes of patients who received the gentamicin lavage versus patients who did not. The main outcome variables were infectious adverse events, CRP level, WBC count, and post-procedural fever (>38 °C). Data are presented as
arithmetic means with standard deviation (SD) and/or medians with first and last deciles/quartiles or interquartile range (IQR). For quantitative variables, two-tailed t-test for paired data (pre vs. post-POEM) and two-tailed t-test for unpaired data (group A vs. group B) were used to test the differences between group A and group B. For qualitative variables, a Fisher exact test was used. The p value below 0.05 was considered as significant.

**Results**

**Patients**

Patients’ characteristics and POEM’s outcome are shown in Table 1. Gender distribution was almost equal, with 68 male patients (54.8%). Mean age was 46.4 years. Most of the patients had type 2 achalasia (68.5%). Dysphagia was present in all patients, with regurgitation as the second most common symptom seen in 89.6% of patients; 87.9% had at least occasional chest pain. A total of 30 patients had prior treatment, mostly balloon dilation. The mean length of procedure (72.2 min ± SD 25.0) and the treatment success (defined as an Eckardt score below 3) at 3 and 6 months did not differ between the two groups (Table 1). We did not experience any technical difficulties during POEM relating to the lavage with gentamicin. All myotomies were completed successfully (regardless of the gentamicin lavage) and all but two (one in each group) entry sites were closed successfully. We placed additional clips in two patients with a leak (esophagogram on POD 1), and their further course was uneventful. There were no readmissions due to post-POEM adverse events.

**Principal outcomes**

The results are shown in Table 2. We did not experience any serious infectious adverse event such as mediastinitis, peritonitis, or abscesses in either group. One patient had to stay in the hospital longer (15 days) due to pleural effusion which had to be drained temporarily, and the patient received a prolonged course of systemic ceftriaxone. The effusion was a consequence of a minor bleeding without the need for blood transfusion. Of note, this patient received a gentamicin lavage, and we consider this patient as the only one with a significant infectious adverse event after POEM.

All remaining patients were discharged on POD 1, 2, or eventually 3. Patients that received gentamicin (group A) stayed for almost one day longer on average than the others (group B) (2.6 ± 1.4 vs. 1.9 ± 0.8, p < 0.001). The longer hospital stay in group A is a consequence of our initial protocol with a scheduled hospital stay until POD 2. Later, we decided to shorten the hospital stay to POD 1, and this was more or less paralleled by our decision not to give the gentamicin lavage.

The percentage of post-POEM fever does not differ between the groups. In both groups, only 10% of patients had a fever.

Post-POEM CRP level (Fig. 1) was elevated in both groups; the median in group A (with gentamicin) was 52.7 mg/L (IQR 34.9) versus 69.5 mg/L (IQR 54.1) in group B (without gentamicin); p = 0.01. Post-POEM WBC count (Fig. 2) differed between groups A and B with statistically significant higher count in group B without gentamicin [median 10.9 × 10^9 (IQR 3.3) group A vs. 12.6 × 10^9 (IQR 3.9) group B; p < 0.01]. As gentamicin may potentially have an impact on kidney function, we investigated serum creatinine before and after (POD 1) POEM. After POEM, serum creatinine level did not significantly change in either group. In patients of group A (with gentamicin), the median creatinine serum levels were 78.5 μmol/L (IQR 26) before versus 74.6 μmol/L (24) after POEM (p = 0.3); the corresponding values in group B were 77.2 μmol/L (23) before versus 75.2 μmol/L (23) (p = 0.6).

Gentamicin lavage did not influence postoperative pain requiring repeated administration of analgesics. Post-

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<thead>
<tr>
<th>Table 1 Patients’ characteristics</th>
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<tr>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Female (N, %)</td>
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<tr>
<td>Eckardt score pre-POEM</td>
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<tr>
<td>Eckardt score post-POEM</td>
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<tr>
<td>Treatment success at 3 months (%)</td>
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<td>Treatment success at 6 months (%)</td>
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<tr>
<td>Length of the procedure (min)</td>
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<tr>
<td>Length of the myotomy (cm)</td>
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<td>BMI pre-POEM</td>
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If not otherwise specified, data represent arithmetical means with SD.
operative pain was present in 13 patients that received gentamicin (out of 58 with available data, 22.4%) and in 19 patients (out of 60, 31.6%) that did not receive gentamicin during POEM ($p = 0.3$).

Discussion

In our retrospective analysis of prospectively collected data, we demonstrated that intraprocedural local administration of gentamicin into the submucosal tunnel has no clinically meaningful role in the prevention of infectious adverse events of peroral endoscopic myotomy (POEM). The rate of infectious adverse events was very low and only one patient (with gentamicin lavage) presented with a significant infectious adverse event (presumably infected pleural effusion). In agreement with other studies [4, 6, 7, 9], we did not experience any severe infectious adverse events such as mediastinitis or peritonitis. Post-POEM fever occurred in approximately 10% of patients in both groups, and fever might not have been a sign of infection but rather an overall reaction of the organism to the procedure. However, patients receiving gentamicin had significantly lower CRP levels and WBC counts, suggesting that a systemic inflammatory response might be lower if gentamicin is used. The difference with regard to CRP levels and WBC counts was, however, clinically negligible.

POEM is a new endoscopic method of treatment for esophageal achalasia. It was firstly performed in 2008 by Prof. Inoue in Japan [4], and since then more than 5000 procedures have been performed worldwide [9]. Surprisingly, POEM has a very good safety profile; the rate of minor adverse events reaches 10–20% (e.g., post-POEM fever, subcutaneous emphysema, inadvertent mucosal injury), serious adverse events are rather rare (e.g., pneumothorax, severe bleeding), and significant infectious adverse events seem extremely rare (e.g., mediastinitis) [6, 7, 9, 10]. So far, no fatal adverse event has been reported in direct conjunction with POEM.

When the POEM program had been started in several centers worldwide, the major fear was about the risk of infections. In fact, a non-sterile endoscope (together with non-sterile accessories) is situated in the mediastinum (or peritoneal cavity) during POEM. Oftentimes, the endoscope is withdrawn from the submucosal tunnel and is introduced into the stomach for desufflation—during which the aspiration of bile (normally present in the stomach) may happen—and bile remnants (from the endoscope) may be irrigated into the submucosal tunnel when the endoscope is again reintroduced into the tunnel. Because of this logical fear of infection, patients receive prophylactic systemic antibiotics before POEM and on POD 1 (ceftriaxone and metronidazole in our center). In the original Inoue’s description, gentamicin submucosal lavage had been performed (in addition to systemic antibiotic administration) in all patients after finishing the myotomy [4, 8]. Because of pain, however, several centers later performed the lavage before starting the myotomy. When we started our POEM program, gentamicin submucosal lavage was a standard part of our protocol.

The rationale for topical gentamicin administration was based on the hypothetical sources of infections—the possible causes could be (1) bacteria from the oral cavity or esophagus (especially Streptococcus viridans, Staphylococcus aureus, and enteric bacilli); (2) remaining water and food residues in the esophagus; (3) intra- or postoperative bleeding, liquid residue in the tunnel, and incomplete closure of the incision. It has been believed that local gentamicin administration into the tunnel might prevent the development of clinically relevant local or systemic infections.

As aminoglycosides, and gentamicin in particular, are active against a broad spectrum of aerobic gram-negative and gram-positive organisms as well as mycobacteria (Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp., *Staphylococcus* spp., and *Streptococcus* spp.).

### Table 2 Main outcomes

<table>
<thead>
<tr>
<th></th>
<th>Total N = 124</th>
<th>Gentamicin+ N = 60</th>
<th>Gentamicin– N = 64</th>
<th>$p$ value</th>
</tr>
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<tbody>
<tr>
<td>Infectious adverse events ($n$, %)</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0 (0.00%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Post-POEM Fever ($n$, %)</td>
<td>12 (10%)</td>
<td>6 (10%)</td>
<td>6 (9.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>67.4 ($±38.2$)</td>
<td>58.4 ($±27.2$)</td>
<td>76.2 ($±44.9$)</td>
<td>0.01</td>
</tr>
<tr>
<td>WBCs ($10^9$ per L)</td>
<td>11.9 ($±3.0$)</td>
<td>11.1 ($±2.5$)</td>
<td>12.6 ($±3.3$)</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Creatinine before/after POEM (µmol/L)</td>
<td>85.4/83.8</td>
<td>84.4/79.8</td>
<td>86.3/87.8</td>
<td>0.8 (before)</td>
</tr>
<tr>
<td>Patients with pain $N$ (%)$^a$</td>
<td>32 (27.1%)</td>
<td>13 (22.4%)</td>
<td>19 (31.6%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>2.3 ($±1.4$)</td>
<td>2.6 ($±1.4$)</td>
<td>1.9 ($±0.8$)</td>
<td>$&lt;0.01$</td>
</tr>
</tbody>
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If not otherwise specified, data represent arithmetical means with SD

*CRP* C-reactive protein, *WBCs* white blood cells

$^a$ Data available from a total of 118 patients
spp. etc.), and gentamicin is the most commonly used antibiotic for prevention of surgical site infection, it has been chosen for topical use in patients undergoing POEM [11]. Compared with systemic antibiotic therapy, the topical (or local) application of antibiotics (especially in the case of potentially toxic gentamicin) has several potential advantages. The benefits of local application include high and sustained concentrations at the site of infections where local physiological changes may hinder the efficacy of systemic antibiotics. In surgery, the selective use of topical antibiotics as surgical prophylaxis is justified in specific procedures (e.g., joint arthroplasty, cataract surgery, breast augmentation, and in selected obese patients undergoing abdominal surgery [12]). Prophylactic local delivery of gentamicin with a novel biodegradable drug carrier system (gentamicin-collagen implant) has been shown to decrease the rate of surgical site infections in several randomized controlled trials, and a gentamicin-collagen sponge might also reduce the sternal surgical site infections in patients following isolated coronary artery bypass [13–15].

Although there is no further evidence to support the use of topical antibiotics to prevent surgical site infection apart from the above-mentioned specific indications, the gentamicin lavage had been used in the majority of centers to prevent infectious adverse events as a consequence of POEM.

As already mentioned, studies and meta-analyses [5, 6, 9, 10] showed that the rate of infectious adverse events after POEM is very low. Our experience was similar and after 50–60 procedures, only one patient developed a "moderate" adverse event with infected pleural effusion (consequence of a hemorrhage), and he received a
prolonged course of systemic antibiotic and fully recovered. Based on these results and after consultations with other experts (Prof. Inoue, Prof. Roesch), we decided to change our protocol and gentamicin has not been used thereafter. Our study shows that gentamicin lavage is safe—it did not cause significant adverse events such as worsening of kidney function or contributing to postoperative pain. Nevertheless, all dispensable drugs should not be administered to patients, not only because of potential adverse events (e.g., severe allergic reaction), but also cost issue (although negligible in case of gentamicin) should be considered. Our study shows that POEM without the gentamicin lavage remained safe without a significant risk of infectious adverse events. We believe that our study provides a useful analysis as several POEM centers continue administering topical gentamicin before starting myotomy (personal communication).

Although there are no studies examining the role of systemic antibiotic in patients undergoing POEM (different antibiotics are used in different centers, timing differs among centers, etc.), there is a general belief that a systemic antibiotic administration is necessary (and not harmful) in patients undergoing POEM. A placebo-controlled trial (antibiotics vs. placebo) is unlikely to be performed. Hypothetically, one cannot rule out the possibility that even systemic antibiotics are not necessary, especially in otherwise healthy patients with uncomplicated POEM procedure.

There are no other studies assessing the role of submucosal lavage with gentamicin. Several published studies even did not mention the use (or no use) of the lavage in addition to systemic antibiotic for prevention of infectious adverse event. Our retrospective analysis is therefore the first addressing the clinical role of topical submucosal lavage with gentamicin in patients undergoing POEM.

Interestingly, we found that patients receiving topical gentamicin had lower WBC count and CRP serum levels. Although the difference between the two groups was not clinically relevant, our results suggest that local gentamicin administration might lead to decreased systemic inflammatory response.

Our study has several limitations. Principally, it is a retrospective analysis and no hemocultures or other microbiological assessments were performed (e.g., cultivation of the fluid from the tunnel) to assess the exact role of gentamicin lavage to prevent bacteremia or infectious adverse events. Furthermore, our sample size is small, and thus our study is underpowered. However, if we consider the rate of infectious adverse events to be 1% and would like to design a prospective study to show a 50% reduction with alpha error 0.05 and beta error 0.2, a total of 9346 patients would have to be enrolled. It is unrealistic that such a prospective study would be performed.

In conclusion, the submucosal lavage with gentamicin in patients undergoing POEM seems to have no clinically meaningful role in the prevention of infectious adverse events.

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Compliance with ethical standards

Disclosures BS Julia Bayer, Dr. Zuzana Vackova, Dr. Hana Svecova, Dr. Petr Stirand, Prof. Julius Spicak and Assoc. Prof. Jan Martinek have no conflict of interest; no financial relationships with any pharmaceutical or device company.

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