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Standard and adjusted criteria for the use of the misoprostol vaginal insert for labor induction: a comparative cohort study

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Abstract

Objective: To compare the efficacy of misoprostol vaginal insert (MVI) for labor induction using standard and adjusted criteria.
Methods: A single-center, comparative cohort study using a consecutive series of pregnant women ≥37/0 weeks undergoing labor induction with either standard criteria for MVI (administration for up to 24 h; MVI-24) or with adjusted criteria (MVI administration for a maximum of 10 h; MVI-10) conducted at a tertiary academic center in Germany. The primary outcomes were the time from start of induction to any delivery and cesarean delivery rate.
Results: A total of 138 women were included in the study, 69 in each group. The mean time from MVI administration to any delivery showed no significant difference between the MVI-24 and MVI-10 groups (954 vs. 969 min, respectively; P = 0.679). The cesarean delivery rate was proportionally lower for the MVI-10 group [39.1% (27/69) vs. 24.6% (17/69); P = 0.10].
Conclusion: The time from induction to delivery with MVI was similar when using standard criteria of up to 24 h of exposure vs. adjusted criteria of up to 10 h of exposure. Although the threshold for statistical significance for cesarean section was not attained, there is nonetheless a considerable difference between the MVI-24 and MVI-10 groups.

Keywords: induction of labor; Misodel®; misoprostol; misoprostol vaginal insert; uterine tachysystole.

Introduction

Globally, induction of labor is one of the most common obstetric procedures [1] and is becoming more frequent, particularly in developed countries [2–6]. The increased rate of labor induction is being driven by an increase in maternal risk factors, such as advanced maternal age [7–9] and high body mass index (BMI), which are associated with an elevated risk for gestational diabetes and preeclampsia [10–12]. Labor induction is also indicated for fetal risk factors, such as placental insufficiency, fetal growth restriction, preterm rupture of membranes and post-term pregnancy [13]. There is extensive evidence that both prostaglandin (PG) E1 (misoprostol) and PGE2 (dinoprostone) are effective agents for cervical ripening and labor induction when compared with each other as well as other induction methods [14, 15].

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic PGE1 analog with gastric acid anti-secretory properties. Oral misoprostol tablets (Cytotec®, Pfizer, New York, NY, USA) are approved to prevent and treat the ulcerogenic effects caused by non-steroidal anti-inflammatory drugs [16]. Misoprostol tablets have been largely used in obstetrics, via either oral or vaginal administration, at lower doses by fragmentation of the 200-µg tablets. Both types of administration have been shown to be more effective at inducing labor vs. placebo [14, 15] as well as vs. dinoprostone but with a higher risk of uterine hyperstimulation [14]. Following concerns over the efficacy and safety of using off-label oral and vaginal misoprostol

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tablet fragments for labor induction, new preparations have been developed, including a controlled-release misoprostol vaginal insert (MVI; Misodel®; Ferring Pharmaceuticals, Saint-Prex, Switzerland) [17]. MVI is approved for induction of labor in women with an unfavorable cervix from 36 weeks of gestation when induction is clinically indicated [18]. MVI is currently widely available in Europe and many other countries. MVI contains 200 µg misoprostol delivered at a rate of approximately 7 µg per hour over a period of 24 h, with maximal plasma concentrations achieved approximately after 4 h [18]. The half-life of misoprostol is between 30 and 45 min [16, 18]. MVI is easily removed, using its integrated retrieval tape, once active labor is achieved [18].

A large randomized, multicenter, double-blind, phase III trial, EXPEDITE, compared 200-µg MVI with a 10-mg dinoprostone vaginal insert (DVI). Women who received MVI (n = 678) had a significantly shorter median time to vaginal delivery vs. DVI (n = 680; 21.5 vs. 32.8 h; $P < 0.001$) without an increase in cesarean delivery rates [26.0 vs. 27.1%; not significant (NS)] [19]. However, more women experienced uterine hyperstimulation with fetal heart rate (FHR) abnormalities in the MVI group vs. DVI group (10.3 vs. 2.6%; $P < 0.05$) [19]. Uterine tachysystole was defined as more than five contractions within 10 min averaged over three consecutive 10-min periods or uterine hypertonus: contraction(s) lasting more than 2 min [19, 20]. Furthermore, various clinical trials for misoprostol, including MVI, have demonstrated that higher doses are associated not only with reduced time to vaginal delivery, but also with increased rates of uterine hyperstimulation [12, 21]. Nevertheless, the 200-µg formulation of MVI has not been shown to have a significant adverse impact on cesarean delivery rates or neonatal outcomes compared with DVI or lower doses of misoprostol (50-µg or 100-µg MVI formulations) [12, 19, 20, 22].

Previously, we presented a pair-matched cohort study comparing MVI with oral misoprostol showing that the time interval between start of induction and any mode of delivery was shorter with MVI; however, the MVI group also had a higher rate of cesarean deliveries [23]. Here, we present findings from two consecutive series of women who had labor induced with either standard (MVI was *in situ* for a maximum of 24 h; MVI-24) or adjusted (MVI was *in situ* for a maximum of 10 h; MVI-10) criteria.

Materials and methods

This comparative cohort study was conducted at our tertiary referral center between October 2014 and January 2016. Written informed consent was obtained from all participating women, and the study was approved by the local Ethics Committee (Medical Association Hamburg, Nr: PV4803-2) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All women included in this study received MVI. The inclusion criteria were a cephalic singleton pregnancy of at least 37 gestational weeks with a modified Bishop score (mBS) ≤5 before induction. The exclusion criteria were hypersensitivity to PGs, uterine scarring, a parity of more than five, any contraindication for a vaginal delivery or chorioamnionitis.

The first series, MVI-24, comprised women who were administered MVI for up to 24 h according to the standard criteria for retrieval provided by the supplier, which were essentially the same as those used in the EXPEDITE study [19]. MVI was placed in the posterior vaginal fornix. After placement, the woman remained in a supine position for 30 min. Continuous cardiotocography (CTG) monitoring was performed from 20 min before to 45 min after MVI insertion to evaluate fetal distress and/or contractions using the International Federation of Obstetrics and Gynecology (FIGO) score. Cervical ripeness was assessed using the mBS. MVI was removed according to the retrieval criteria (Table 1). If uterine tachysystole, defined as more than five contractions within 10 min averaged over three consecutive 10-min periods, combined with FHR abnormalities occurred, intravenous Fenoterolhydrobromid (Partusisten®, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was used for tocolysis. In this group, MVI was removed no later than 24 h after its application, and no repeated application was performed.

In February 2015, we changed the criteria for MVI administration in our center. A second series of women eligible for pharmacological

Table 1: Retrieval criteria for the MVI-24 and MVI-10 groups.

Retrieval criteria	Misoprostol vaginal insert – 24 h group	Misoprostol vaginal insert – 10 h group
Maximum amount of time MVI *in situ*	24 h	10 h
Retrieval indicated if		
Contraction frequency	Three or more contractions (i.e. at least three) every 10 min lasting at least 45 s	One or more contractions (i.e. at least one) per 5 min lasting at least 45 s
Cervical dilation	And/or cervical dilatation was ≥4 cm regardless of contraction frequency	And/or cervix was completely effaced or dilatation was ≥1 cm regardless of contraction frequency
Further intervention	And/or signs of fetal or maternal complications requiring intervention	And/or signs of fetal or maternal complications requiring intervention

induction of labor were included, in whom MVI was administered for up to 10 h (MVI-10 group). In this group, removal of MVI was indicated at an earlier stage of labor compared to MVI-24 (Table 1). The maximum administration of 10 h was chosen after analysis of the MVI-24 group data, which showed an increase of cesarean delivery rate when MVI was administered for more than 10–12 h.

In both the MVI-24 and MVI-10 groups, if induction with MVI did not lead to active labor, women were further induced with pre-delivery oxytocin, vaginal dinoprostone or oral misoprostol. When necessary, pre-delivery oxytocin was administered at least 30 min after the removal of MVI, and dinoprostone or misoprostol at least 6 h after removal of MVI.

Primary outcomes were the time interval from MVI administration to any delivery and the rate of cesarean section.

Secondary outcome measures were the rate of vaginal birth, time interval from MVI administration to vaginal delivery, number of women who required additional PG agents, pre-delivery oxytocin use and rate of uterine tachysystole requiring treatment. The proportion of any delivery achieved in 48 h was also assessed in a *post-hoc* analysis.

The data were collected from the hospital's obstetric database, including demographics and baseline characteristics. All descriptive and inferential statistical analyses were performed using IBM SPSS Statistics 22 (Armonk, NY, USA). Delivery mode (vaginal or cesarean delivery) within 48 h was compared between groups using the chi-squared test. Time to delivery was analyzed using the Mann-Whitney *U*-test, log-rank test or Grey's test. Other outcomes were assessed using Fisher's exact test. An alpha error of $\alpha < 0.05$ indicated statistical significance.

Univariate analysis based on the chi-squared test or Pearson's correlation coefficient identified independent factors that were significantly associated with the mode of delivery. These factors (maternal age, ethnicity, BMI at the time of induction, parity, gestational age, Bishop score and birth weight) were used in an integrated logistic regression model to estimate whether the medication was still a significant predictor of the delivery mode after the inclusion of other potential predictors as covariates.

Ethical approval

The local Ethics Committee approved the protocol, participant consent form, patient information sheet and study brochure (PV4803-2, August 4, 2015). The study was performed in accordance with the ethical conduct standards that originate from the Declaration of Helsinki and with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Tripartite Guideline on Good Clinical Practice. Clinical Trial Registration was at ClinicalTrials.gov – NCT03016208.

Results

A total of 138 women, 69 women in each group, were included in this study. Both the MVI-24 and MVI-10 groups had similar demographics in terms of mean maternal age, nationality, parity and gestational age (Table 2). The mean maternal age was 31 years in both groups and the majority of women were nulliparous (MVI-24: 74%; MVI-10: 77%). Reasons for induction of labor were similar between the two groups, except that there were more women with diabetes and fewer women with preeclampsia/hypertension in the MVI-24 vs. MVI-10 groups. All but four women in the MVI-24 group (6%) and seven women in the MVI-10 group (10%) included in the analysis achieved any delivery within 48 h of the start of induction. Women who were still pregnant after 48 h delivered after a maximum of 78 h.

Table 2: Demographics and baseline characteristics.

Characteristics	Misoprostol vaginal insert – 24 h group (n = 69)	Misoprostol vaginal insert – 10 h group (n = 69)
Maternal age, years	31.0 ± 6.0	31.1 ± 5.5
Nationality		
Middle European	56 (81.2)	54 (78.3)
Immigrant background	13 (18.8)	15 (21.7)
Parity		
Nulliparous	51 (74)	53 (77)
Parous	18 (26)	16 (23)
Gestational age, weeks	41.0 ± 1.3	40.6 ± 1.4
Reasons for induction[a]		
Prolonged pregnancy (40 or more weeks)	34 (49.3)	35 (50.7)
Rupture of membrane	10 (14.5)	7 (10.1)
Diabetes	12 (17.4)	6 (8.6)
Oligohydramnios	11 (15.9)	9 (13.0)
Maternal fatigue	7 (10.1)	6 (8.6)
Preeclampsia/ hypertension	4 (5.8)	9 (13.0)
Other	16 (23.0)	16 (23.0)
BMI, kg/m^2	30.8 ± 5.8	30.5 ± 5.5
Baseline modified Bishop score	2.2 ± 1.6	2.5 ± 1.7
0	15 (21.0)	12 (16.9)
1	9 (12.9)	9 (13.0)
2	12 (17.7)	13 (19.5)
3	18 (25.8)	16 (23.4)
4	11 (16.1)	10 (14.3)
5	4 (6.5)	9 (13.0)

BMI, body mass index. Data are presented as mean ± standard deviation or n (%). [a]More than one reason was possible.

Table 3 shows the primary and secondary outcomes of the study. For the primary endpoint, there was no significant difference in the median time interval from MVI administration to any delivery [MVI-24: 954 min, 95% confidence interval (CI): 628–1431 min; MVI-10: 969 min, 95% CI: 642–1479; P = 0.679]. Figure 1 shows the cumulative incidence for time from MVI administration to any delivery for both treatments. There was no significant difference in

Table 3: The primary and secondary outcomes after induction with MVI-24 and MVI-10.

Parameter	Misoprostol vaginal insert – 24 h group n=69	Misoprostol vaginal insert – 10 h group n=69	P-value	Effect size	95% CI	Tests for P-value
Time from induction to delivery, min						
All deliveries	954 (628–1431)	969 (642–1479)	0.679	na	na	MW-U
Vaginal	1570 (791, na)	1198 (674–4687)	0.131	na	na	Grey's
Cesarean deliveries	27 (39.1)	17 (24.6)	0.100	na	na	Fisher's
Uterine tachysystole requiring tocolysis	18 (26.1)	8 (11.6)	0.049[a]	RR=2.250	1.049–4.826	Fisher's
Additional prostaglandins used for IOL	4 (5.8)	13 (18.8)	0.036[a]	RR=0.308	0.106–0.897	Fisher's
Pre-delivery oxytocin use	21 (30.4)	35 (50.7)	0.024[a]	RR=0.60	0.392–0.919	Fisher's

Data are presented as median (95% confidence interval) or n (%). [a]Statistically significant (P<0.05). na, not available; IOL, induction of labor; RR, risk ratio; CI, confidence interval; MW-U, Mann-Whitney *U*-test; Grey's, Grey's test; Fisher's, Fisher's exact test.

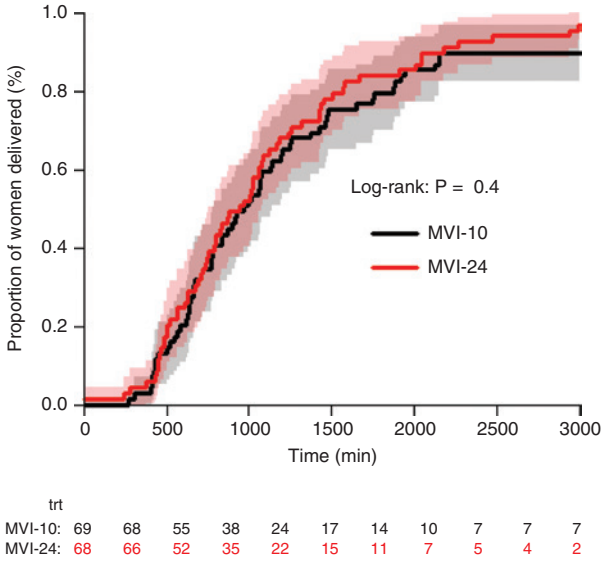

Figure 1: Cumulative incidence of all deliveries within the first 48 h after induction of labor.
MVI-24 (red); MVI-10 (black). Pink and gray shading indicate pointwise 95% confidence intervals.

the median time from MVI administration to vaginal delivery between the MVI-24 (1570 min, CI: 791–not available) and the MVI-10 groups (1198 min, CI: 674–4687; P=0.131).

Figure 2 shows a competing risk plot for time from MVI administration to either vaginal or cesarean delivery for both groups. The cesarean delivery rate was 39.1% (27/69 women) vs. 24.6% (17/69) for the MVI-24 and MVI-10 groups, respectively (P=0.10). For cesarean deliveries, the gradient of the slope was initially steeper for the MVI-24 group, indicating that more cesarean deliveries were performed earlier after the start of induction compared with the MVI-10 group. The most common reasons for cesarean delivery in both the MVI-24 and MVI-10 groups were FHR abnormalities [17/27 (63.0%) and 10/17 (58.8%), respectively], followed by prolonged dilatation or arrest of descent [6/27 (22.2%) and 4/17 (23.5%), respectively].

After testing for potential confounding variables (maternal age, ethnicity, BMI at the time of induction, parity, gestational age, mBS and birth weight), only parity was significantly correlated with the mode of delivery (r=0.235, P=0.006). Parity and MVI protocol (MVI-24 vs. MVI-10) were entered into a logistic regression model to predict the mode of delivery. The two MVI protocols had no significant impact on the aforementioned delivery outcome, beyond the effects of parity (P of the regression model=0.056; adjusted 95% CI: 0.98–4.5).

Uterine tachysystole requiring tocolysis occurred significantly more often in the MVI-24 group [18/69 (26.1%)] than in the MVI-10 group [8/69 (11.6%)], P=0.049, with a relative risk (RR) of 2.250 (95% CI: 1.049–4.826).

The need for additional PGs was significantly less in the MVI-24 group [4/69 (5.8%)] than the MVI-10 group [13/69 (18.8%); P=0.036] with an RR of 0.308 (95% CI: 0.106–0.897). Similarly, fewer women in the MVI-24 group were administered pre-delivery oxytocin compared with the MVI-10 group [21/69 (30.4%) vs. 35/69 (50.7%); P=0.024; RR 0.60 (95% CI: 0.392–0.919)].

Discussion

We previously assessed the 69 consecutive women who had labor induced with MVI after its introduction to our unit and compared its efficacy and safety with a pair-matched group of women who had been induced with oral misoprostol [23]. In our setting, MVI significantly shortened the time from start of induction to delivery compared with oral misoprostol but we were concerned that the MVI group also had a higher cesarean delivery rate and worse neonatal outcomes [23]. Although we do

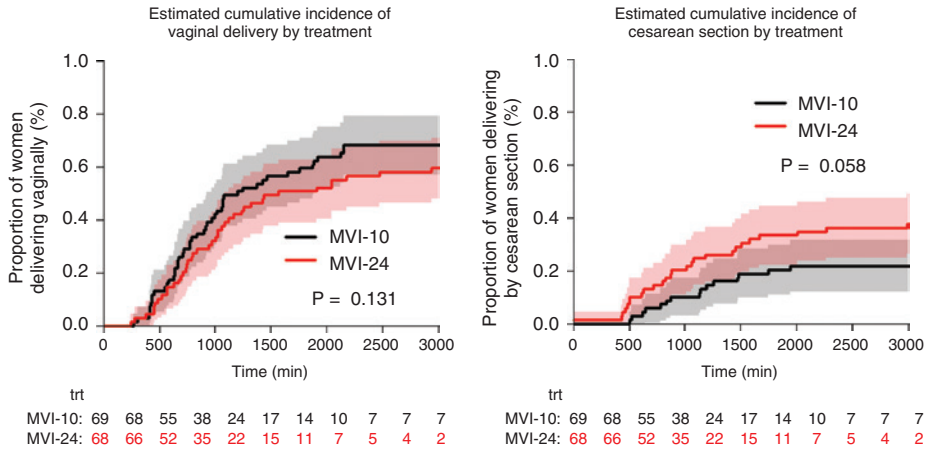

Figure 2: Competing risk plot depicting the cumulative incidence of vaginal and cesarean deliveries within the first 48 h after induction of labor.
MVI-24 (red); MVI-10 (black). Pink and gray shading indicates point-wise 95% confidence intervals.

not know whether these findings were due to our relative inexperience with MVI compared with oral misoprostol or an actual higher risk of cesarean delivery and worse neonatal outcomes, we started using a modified protocol for labor induction with MVI, MVI-10. The adjusted protocol used a maximum of 10 h of exposure to MVI as we discerned that there was an increase in the rate of cesarean deliveries after 10–12 h of exposure to MVI. We compared the time from start of induction to delivery as well as the cesarean section rate for the women who had been treated with MVI using either the standard (MVI-24) or adjusted protocol (MVI-10).

We found no significant difference between the MVI-24 and MVI-10 groups in the time from start of induction to delivery (approximately 16 h in both groups), and the difference between the median values was only 14 min. However, significantly fewer women in the MVI-24 vs. MVI-10 groups received additional PGs and pre-delivery oxytocin. In addition, while we were not able to attain the threshold for statistical significance for cesarean section, there was nonetheless an appreciable difference between the MVI-24 and MVI-10 groups. The most common indication for cesarean delivery was FHR abnormalities for both groups. The rate of uterine tachysystole requiring tocolysis was significantly higher with MVI-24 vs. MVI-10, which can be explained by a higher exposure to misoprostol in the MVI-24 group.

The interpretation of our study results is limited due to the rather small number of women included. Still, they address concerns regarding maternal and neonatal safety when using the MVI, as previously reported [23]. To date, published clinical data that compare different regimes of MVI applications are lacking. However, it may be possible to reduce the risk of cesarean delivery by using adjusted criteria for removal instead of the licensed criteria by the manufacturer. Our study is the first to address this issue and promote further research in this area. However, a limitation of our study is that the two protocols for MVI were not assessed in parallel, but consecutively. This means that the clinical experience gained while we were using the MVI-24 induction criteria may have improved outcomes for the women in the MVI-10 group. Furthermore, we changed simultaneously three variables requiring MVI retrieval in the adjusted MVI-10 criteria: (1) maximum duration of the MVI *in situ* (decreased from 24 to 10 h); (2) the frequency of contractions decreased (from three or more contractions in 10 min to one or more contractions in 5 min); and (3) cervical dilation (from at least 4 cm dilated to either completely effaced or at least 1 cm dilated). As such, we do not know whether it was a combination of these changes or just one that influenced our results. It may be possible to reduce the need for additional induction agents required in the MVI-10 group by further modifying the MVI removal criteria.

Nevertheless, our study highlights the need for careful utilization of the MVI for induction of labor. Recent guidance from the Swiss Society of Gynecologists and Obstetricians also provides preference for the use of the MVI when inducing labor in women with diabetes, preeclampsia or hypertension (without fetal growth restriction) over misoprostol tablet fragments due to the instability of misoprostol in the presence of moisture and lack of standardization (dose and frequency of administration) when using misoprostol tablet fragments [24]. Importantly, the MVI should only be used to induce labor in a setting with experienced staff capable of managing uterine tachysystole with FHR involvement, and with the facilities to perform an emergency cesarean delivery. If uterine tachysystole

occurs, then the MVI should be removed immediately and continuous CTG should be used to monitor for FHR abnormalities, as per induction of labor guidelines [24–26]. The half-life of misoprostol is 30–45 min [16, 18], and therefore the time to uterine tachysystole resolution will be longer compared with PGE2 [19, 20]. In addition, MVI should only be administered to women with no contraindications, which includes a suspicion or evidence of fetal compromise, such as the presence of meconium or non-reassuring FHR, prior to induction [18, 24]. Our study included women with an mBS of 5; nonetheless, it is important to note that the product label states that MVI should be used cautiously in women with an mBS >4.

Future comparisons of protocols that use MVI for induction of labor would ideally use a randomized, prospective, double-blind trial design that investigates the use of two or more different MVI induction criteria. However, a double-blind trial design would not be possible for the two protocols assessed in our study due to the different criteria for MVI retrieval.

Conclusion

Misoprostol is a highly effective uterotonic agent, but can potentially also cause maternal and perinatal adverse events. Therefore, evaluation of the efficacy and adverse effects of the MVI following modification of the application criteria was necessary. Our data show that MVI is similarly effective for induction of labor for both modified criteria and standard criteria as stated on the label. However, use of MVI following modified criteria demonstrated a reduction in adverse effects, a finding which may further enhance maternal and fetal safety while maintaining the positive uterotonic effect.

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Author contributions: PS, AB, MD and WH conceived the study. MD enrolled the participants. AB and MD collected the data. AB, MD, HH and TFD analyzed the data. AB, MD, HH and PS interpreted the data. AB, MD and PS wrote the article. All authors critically reviewed and amended multiple drafts of the manuscript's concept and outline, as well as the full manuscript, and all authors approved the final draft of the manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Conflicts of interest: PS received consultation fees from Ferring Pharmaceuticals with regard to prostaglandin vaginal inserts. None of the other authors of this study have any relevant conflicts of interest (financial, personal, political, intellectual or religious) to disclose. The full disclosure of interests is available to view online as supporting information. The authors have had full control of the primary data and they allow the journal to review the data if requested.

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Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. During this study, no animals were used by any of the authors. This study is a collaboration between Asklepios Hamburg and Charité – University Medical Center Berlin. It is part of the medical thesis of the first author, who is registered and supervised at Charité – University Medical Center Berlin. However, patients were recruited at Asklepios Clinic Barmbek, Hamburg; therefore, the ethical committee was chosen there.

Supplementary material: Ethical committee approval and grant contract.

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