MAYO CLINIC

Effects of Sugammadex* on Time of First Postoperative Bowel Movement: A Retrospective Analysis

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Abstract

Objective: To determine whether time to first postoperative bowel movement after intraperitoneal surgery differs among neuromuscular blockade reversal with either anticholinesterase/anticholinergic combination vs sugammadex.

Patients and Methods: Sugammadex was introduced to our practice in October 2016. Patients were identified who underwent intraperitoneal surgery between January 1, through June 30, 2016, and January 1 through June 30, 2017, and received aminosteroid neuromuscular blockade for paralysis. Reversal was initiated with neostigmine, coadministered with glycopyrrolate (neostigmine/glycopyrrolate) for control participants and sugammadex for patients. Time to first bowel movement was determined from nursing documentation for study cohorts (2016 and 2017). We compared times to first bowel movement between cases and controls using raw and inverse probability of treatment weighting (IPTW) analyses.

Results: In the 2016 cohort, 2583 received neostigmine/glycopyrrolate. Of 2750 patients in 2017, sugammadex reversal technique was administered to 1500 patients and neostigmine/glycopyrrolate to 1250 participants. Without weighting, the groups were relatively balanced for most baseline characteristics, and after IPTW, all standardized differences were <0.035. In comparison with the 2016 and 2017 controls, sugammadex treatment was associated with faster occurrence of first bowel movement. For 2016, unweighted hazard ratio (HR) (95% confidence interval [CI]) was 1.35 (1.21-1.51) ($P<.001$). After IPTW, HR (95% CI) was 1.27 (1.12-1.43) ($P<.001$). For 2017, unweighted HR (95% CI) was 1.51 (1.31-1.72) ($P<.001$); after IPTW, it was 1.25 (1.08-1.45) ($P=.003$).

Conclusion: Patients undergoing intraperitoneal surgery who had aminosteroid neuromuscular blockade reversal with sugammadex had earlier first postoperative bowel movement than patients with reversal through neostigmine/glycopyrrolate.

 ■ Mayo Clin Proc Inn Qual Out 2019;3(3):294-301

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Postoperative gastrointestinal tract dysfunction commonly occurs following intraperitoneal surgery, causing patient discomfort and increased health care resources.[1] Despite perioperative modifications to reduce postoperative gastrointestinal tract dysfunction, it continues to be a major concern.[2,3] Factors commonly ascribed to postoperative gastrointestinal tract dysfunction include surgical stress response, bowel dysfunction secondary to operative trauma, and opioid analgesics.[4]

One overlooked factor that may influence postoperative bowel function is the medication to reverse nondepolarizing neuromuscular blocking agents (NMBAs). Traditionally, anticholinergic agents (eg, neostigmine) are used. These have muscarinic properties, which effectively promote postoperative bowel activity.[5] However, other aspects of muscarinic activity are undesirable (bradycardia, increased oral secretions, abdominal cramps); thus, an anticholinergic agent is coadministered against these effects.[6] Anticholinergic agents decrease bowel function[7] but appear to only modestly counteract neostigmine promotility effects.[6,8,9]

Sugammadex is a novel reversal agent for aminosteroid NMBAs (rocuronium, vecuronium), with reversal through encapsulation and has no muscarinic activity and no requirement for anticholinergic drug coadministration.[10]

However, only 2 small studies have assessed whether the NMBA reversal agent influences postoperative bowel function.[11,12]

In October 2016, sugammadex was introduced to our institution, which has a high-volume surgical practice and a robust information technology infrastructure. These characteristics allow for sophisticated retrospective evaluation of perioperative outcomes (Table 1).[13,14] In this study, we examine whether time to first bowel movement differs between patients administered sugammadex vs neostigmine/glycopyrrolate for the reversal of aminosteroid NMBAs.

METHODS

The Mayo Clinic Institutional Review Board approved this study (protocol No. 17-003136, approved on April 25, 2017). Consistent with Minnesota Statute 144.295, all

TABLE 1. Characteristics of Patients Undergoing Intraperitoneal Surgery With Aminosteroid Neuromuscular Blockade Reversed With Neostigmine/Glycopyrrolate or Sugammadex

	Reversal Agent		
	Neostigmine/Glycopyrrolate[b]		Sugammadex
Characteristics[a]	2016 (n=2583)	2017 (n=1250)	2017 (n=1500)
Age, mean (SD), y	55.2 (16.3)	52.9 (17.2)	57.0 (16.0)
Sex			
Male	988 (38.3)	539 (43.1)	601 (40.1)
Female	1595 (61.7)	711 (56.9)	899 (59.9)
BMI, mean (SD), kg/m^2	29.6 (8.2)	30.1 (8.2)	29.0 (7.3)
Current smoker	180 (7.0)	80 (6.4)	90 (6.0)
Impaired mobility	233 (9.0)	104 (8.3)	106 (7.1)
CCI, mean (SD)	4.3 (3.4)	4.0 (3.4)	4.6 (3.4)
Obstructive sleep apnea	531 (20.6)	278 (22.2)	279 (18.6)
Home use of drug			
Opioids	1247 (48.3)	652 (52.2)	659 (43.9)
Benzodiazepines	523 (20.2)	244 (19.5)	293 (19.5)
Gabapentinoids	213 (8.2)	118 (9.4)	125 (8.3)
Surgical approach			
Open	1308 (50.6)	578 (46.2)	742 (49.5)
Laparoscopic	1275 (49.4)	672 (53.8)	758 (50.5)
Duration of surgery, mean (SD), min	169 (109)	165 (112)	173 (113)
Perioperative medications			
Opioid, mean (SD), IVME mg	34.5 (16.5)	31.4 (16.5)	32.2 (16.0)
Neuraxial opioid	414 (16.0)	216 (17.3)	286 (19.1)
Propofol induction	2554 (98.9)	1240 (99.2)	1438 (98.9)
Midazolam	1304 (50.5)	473 (37.8)	714 (47.6)
Acetaminophen	1580 (61.2)	663 (53.0)	1040 (69.3)
NSAID	1365 (52.8)	561 (44.9)	919 (61.3)
Gabapentin	872 (33.8)	260 (20.8)	643 (42.9)
Ketamine	1357 (52.5)	704 (56.3)	992 (66.1)
Scopolamine	17 (0.7)	10 (0.8)	16 (1.1)
Isoflurane	994 (38.5)	287 (23.0)	496 (33.1)
Perioperative fluids			
Colloid	575 (22.3)	265 (21.2)	272 (18.1)
Transfusion	148 (5.7)	80 (6.4)	95 (6.3)
Crystalloid, mean (SD), L	2.62 (1.54)	2.28 (1.57)	2.45 (1.51)

[a]Values are presented as number and percentage of patients unless specified otherwise.
[b]Combination of neostigmine with glycopyrrolate.
BMI = body mass index; CCI = Charlson Comorbidity Index; IVME = intravenous morphine equivalents; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation.

patients in this study provided prior authorization for research use of their health records.

Clinical Practice

This study is representative of a high-volume surgical practice within a major tertiary academic institution. The anesthesia care model consists of an attending anesthesiologist who supervises the anesthesia administration by certified nurse anesthetists, student nurse anesthetists, and resident anesthesiologists. Decisions regarding NMBA use are at the attending anesthesiologist's discretion, but vecuronium is used most frequently, with rocuronium being the second most commonly used agent. A peripheral nerve stimulator monitors muscle relaxation with a train-of-four stimulation pattern. Before the introduction of sugammadex on October 1, 2016, the NMBA reversal technique was neostigmine coadministered with glycopyrrolate (neostigmine/glycopyrrolate). Afterward, no restrictions were made on sugammadex use, and the choice of NMBA reversal technique was at the attending anesthesiologist's discretion.

Following anesthesia recovery, such patient-care measures as patient intake of intravenous fluids, oral intake, and output from drains and catheters are recorded by nursing staff. This information includes the date and time when the patient defecates.

Postoperatively, the nature of the procedure and surgical pathology influence whether a nasogastric tube is placed and therefore, how long it remains. For the majority of elective biliary, distal foregut, midgut, and hindgut procedures an orogastric tube is used intraoperatively and removed at case completion. The following medications are then started the day of surgery and continued in all patients: docusate sodium 100 mg every 12 hours, senna 17.2 mg orally every 12 hours, polyethylene glycol 3350 17 gm orally every 12 hours, with bisacodyl suppository 10 mg per rectum daily as needed if no bowel movement. In the event the patient remains endotracheally intubated after an elective procedure, an orogastric or nasogastric tube is left in place and is used for this regimen until the patient is extubated. A preoperative lavage bowel prep or enema will rarely be used before certain distal colon cases, but not routinely.

In the event of urgent or emergent intraperitoneal cases, the nature of the surgical procedure dictates the anticipated period of ileus and the need for gastric decompression. Also, with damage-control procedures when intestinal continuity is not restarted, oral or enteric medication administration is avoided. Because of case acuity, a preoperative bowel preparation is not possible. If vasopressors or inotropes have been required for patient support after these urgent or emergent procedures, once these medications have been discontinued, bowel-regimen agents will be started. Enteral nutrition will be started once nasogastric output is low.

Patient Selection

Participant selection included adult surgical patients who underwent general endotracheal anesthesia for intraperitoneal surgery. The patients received aminosteroid NMBA treatment, which was reversed with either neostigmine/glycopyrrolate or sugammadex. Patients were excluded if they were administered a benzylisoquinolinium NMBA or their paralysis was not reversed.

Study Design

This study was designed to assess possible associations between the introduction of sugammadex and the return of postoperative bowel function. To accomplish this goal, patients paralyzed with aminosteroid NMBA for intraperitoneal surgery, who received sugammadex for the reversal technique, were compared with 2 different cohorts of patients with aminosteroid NMBA paralysis that was reversed with neostigmine/glycopyrrolate. One cohort was selected from a contemporaneous sample, and the second cohort was a sample from the same calendar months of the preceding year. The decision to use 2 comparison cohorts was made in order to minimize 2 sources of potential confounders. Using a comparison cohort from the previous year will minimize the impact of selection bias of choice of reversal technique. Using a contemporaneous cohort will minimize the potential bias owing to unknown other practice changes that could influence bowel-function recovery.

The anesthesia database was queried on 2 separate 6-month periods: January 1, through June 30, 2016, and January 1, through June

Mayo Clin Proc Inn Qual Out ■ September 2019;3(3):294-301 ■ https://doi.org/10.1016/j.mayocpiqo.2019.06.003
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FIGURE 1. Weighted (**solid square**) and unweighted (**open square**) standardized differences between sugammadex group and the neostigmine with glycopyrrolate (control) groups are presented for each baseline characteristic. Points plotted on the left are for comparisons using 2016 controls and points plotted on the right are for 2017 controls. A vertical reference line is included at 0.1, which is commonly used to represent adequate balance between groups. NSAID = nonsteroidal anti-inflammatory drug.

30, 2017. Adult surgical patients who met study inclusion criteria were identified. The electronic health records of these patients were abstracted for clinical and perioperative characteristics, as previously described.[13,14] Nursing records were abstracted to determine the date and time of the first postoperative bowel movement. Time to first bowel movement was calculated as the time from the end of surgery to the first bowel movement.

Statistical Analysis

Patients were categorized into 3 study groups: neostigmine/glycopyrrolate 2016, neostigmine/glycopyrrolate 2017, and sugammadex. Patient and procedural characteristics were summarized according to study group using mean (standard deviation [SD]) for continuous variables and frequency count and percentage for categorical variables. The primary outcome of interest was the time to first bowel movement and the secondary outcome of interest was hospital length of stay (LOS). Separate analyses were performed to compare the sugammadex group with each neostigmine/glycopyrrolate (control) group. In addition to unadjusted comparisons, propensity-adjusted analyses were performed with inverse probability of treatment weighting (IPTW) to adjust for potential confounding. Logistic regression was used to calculate propensity

scores for sugammadex use, with all patient and procedural characteristics included as explanatory variables. For each covariate, the standardized mean difference among treatment groups was calculated before and after propensity score adjustment in order to assess whether the propensity approach was able to adequately control for potential confounding.

Time to first bowel movement was compared among groups with use of proportional hazards regression and findings were presented as hazard ratio (HR) and corresponding 95% confidence interval (CI). For these analyses, an HR greater than 1 corresponds to a shorter time to first bowel movement in patients administered sugammdex vs neostigmine/glycopyrrolate. Hospital length of stay (LOS) was compared among groups through the Wilcoxon rank sum test. For IPTW analysis, hospital LOS was transformed through Van der Waerden method to obtain normal scores that then were compared among groups in an analysis for generalized estimating equations with IPTW and a robust variance. In all cases, 2-tailed tests were performed, and *P* less than .05 denoted statistical significance.

RESULTS

During the 2016 study time frame, 2583 adult surgical patients underwent intraperitoneal surgery that involved paralysis with an aminosteroid NMBA and reversal with neostigmine/glycopyrrolate. During the 2017 study time frame, 2750 patients met study criteria, of whom 1500 underwent NMBA reversal with sugammadex and 1250 with neostigmine/glycopyrrolate. An additional 22 patients were excluded because they received both sugammadex and neostigmine/glycopyrrolate. Vecuronium was used in 4390 cases and rocuronium in 1050 cases. The mean (SD) neostigmine dose was 4.0 (0.9) mg; glycopyrrolate, 0.6 (0.2) mg and the ratio (neostigmine/glycopyrrolate doses) was 6.9 (2.2). For sugammadex, the mean (SD) dose was 176 (56) mg. Table 1 summarizes patient and procedural characteristics. Without weighting, clinical characteristics were relatively balanced between the 2016 and 2017 control groups and the 2017 group. After IPTW, all SDs were less than 0.035 (Figure 1).

Kaplan-Meier curves for time to first postsurgical bowel movement are presented in Figure 2. Compared with both 2016 and 2017 control groups, sugammadex was associated with earlier time to first bowel movement (Table 2). Results showed that compared with the sugammadex group, the 2016 neostigmine/flycopyrrolate control group unweighted (HR [95% CI], 1.35 [1.21-1.51]; *P*<.001) and after IPTW (HR [95% CI], 1.27 [1.12-1.43]; *P*<.001) and the 2017 neostigmine/glycopyrrolate control group unweighted (HR [95% CI], 1.51 [1.31-1.72]; *P*<.001) and after IPTW (HR [95% CI], 1.25 [1.08-1.45]; *P*=.003). A supplemental analysis was performed that only included patients who received neostigmine/glycopyrrolate. From this analysis, which adjusted for variables used in the propensity weighting, we found that a higher ratio between neostigmine/glycopyrrolate (ratio of neostigmine to glycopyrrolate greater than 7.0 versus less than 7.0) was associated with a shorter time to first bowel movement (HR [95% CI], 1.027 [1.001, 1.053]; p=0.042).

Hospital LOS did not differ significantly between the sugammadex group (median [interquartile range {IQR}], 3 [2-6] days) and the 2016 control group (median [IQR], 3 [2-6] days; unweighted, *P*=.12; IPTW, *P*=.06) and the 2017 control group (median [IQR], 3 [2-6] days; unweighted, *P*=.89; IPTW, *P*=.12).

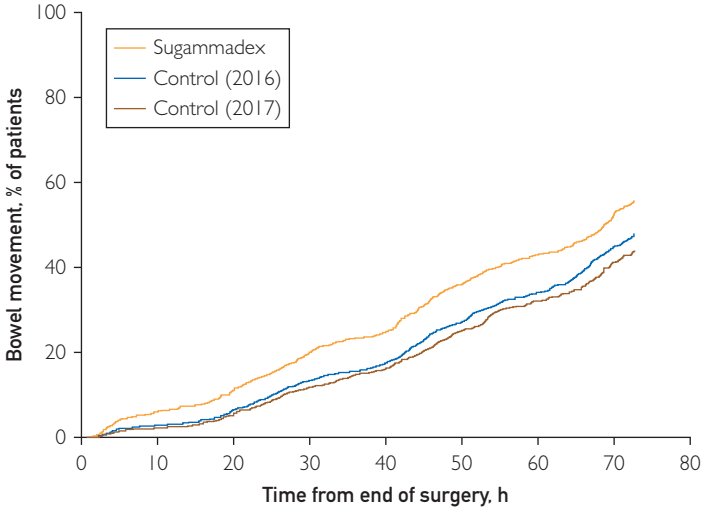

FIGURE 2. Kaplan-Meier curves summarizing the cumulative percentage of patients with bowel movements over the first 72 postoperative hours.

Mayo Clin Proc Inn Qual Out ■ September 2019;3(3):294-301 ■ https://doi.org/10.1016/j.mayocpiqo.2019.06.003
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TABLE 2. Outcomes of Patients Undergoing Intraperitoneal Surgery With Aminosteroid Neuromuscular Blockade Reversed With Neostigmine/Glycopyrrolate or Sugammadex

Outcome	Reversal agent		
	Neostigmine/Glycopyrrolate[a]		Sugammadex
	2016 (n=2583)	2017 (n=1250)	2017 (n=1500)
Time to postoperative bowel movement, HR (95% CI), h[b]			
24	9.5 (8.3-10.7)	8.4 (6.7-10.0)	14.9 (13.0-16.8)
48	26.3 (24.3-28.3)	24.1 (21.3-26.9)	35.2 (32.3-38.0)
72	47.6 (45.0-50.1)	43.6 (39.9-47.2)	55.6 (52.1-58.8)
Hospital LOS, d[c]			
Median (IQR)	3 (2-6)	3 (2-6)	3 (2-6)
≤1	597 (23.1)	245 (19.6)	295 (19.7)
2-4	1090 (42.2)	546 (43.7)	661 (44.1)
5-7	513 (19.8)	250 (20.0)	296 (19.7)
≥8	383 (14.8)	209 (16.7)	248 (16.5)

[a]Combination of neostigmine with glycopyrrolate.

[b]Kaplan-Meier method was used to obtain the estimate of the cumulative percentage of patients with bowel movement at 24, 48, and 72 hours; proportional hazards regression, to compare the time to first bowel movement between groups.

[c]Unweighted comparisons of hospital LOS were performed using rank sum test. For IPTW analysis, hospital LOS was transformed through Van der Waerden method to obtain normal scores that were then compared among groups in an analysis using generalized estimating equations with IPTW weights and a robust variance.

HR = hazard ratio; IPTW = inverse probability of treatment weighting; IQR = interquartile range; LOS = length of stay.

DISCUSSION

The major finding of this study is that use of sugammadex to reverse aminosteroid NMBAs following intraperitoneal surgery was associated with earlier time to first bowel movement compared with the traditional reversal technique with neostigmine/glycopyrrolate. This finding was observed in comparisons with separate contemporaneous and antecedent control cohorts. We conducted 2 comparisons to reduce potential sources of selection bias and bias from unmeasured practice changes over time. At baseline, both control cohorts were relatively well balanced with the sugammadex cohort; after propensity adjustment, all other differences were negligible. The magnitude and consistency of these observations from both cohorts and from the raw and adjusted analyses support the hypothesis that bowel function recovers earlier after sugammadex reversal. Our finding has potentially important implications for contemporary emphasis on enhanced postoperative recovery, including early return of bowel function.[15,16]

Despite earlier time to first bowel movement, an association was not observed between reversal technique and hospital LOS. Various medical and social factors can influence time to hospital discharge, which could obscure beneficial effects of an earlier bowel movement. In addition, LOS was determined in day increments, and therefore our data lack the granularity to show a decreased LOS if the benefit of an earlier bowel movement was in hours. However, the lack of associated changes in LOS suggest the clinical implications of early time to first bowel movement requires further study.

The admixture of muscarinic and anticholinergic drugs to reverse NMBAs has long been advocated to mitigate muscarinic-mediated bradycardia and other adverse effects.[6,17] The promotility effects of muscarinic agents on the gastrointestinal tract and the antimotility effects of anticholinergic agents are historical medical knowledge.[18,19] However, atropine incompletely mitigates the promotility effects of neostigmine.[6,8,9] The effects of glycopyrrolate on delayed gastric emptying are greater than atropine.[7] One small study found that glycopyrrolate had a similar effect as atropine in mitigating the promotility effects of neostigmine.[9] A study of neostigmine use to promote bowel activity among patients with spinal cord stimulators found that the combination of neostigmine/glycopyrrolate did not negate the promotility effects of neostigmine.[20] However, the cumulative effect of muscarinic and

anticholinergic combinations on gastrointestinal tract function compared with sugammadex has not been extensively studied.

Because sugammadex has neither muscarinic nor anticholinergic properties[10] and has a low distribution volume,[21] it is unlikely to possess gastrointestinal tract effects. Comparative evidence regarding function of the gastrointestinal tract after sugammadex or neostigmine administration is limited to 2 small randomized studies.[11,12] Sen et al[11] did not find an association between NMBA reversal technique and time to first flatus or bowel movement following thyroid surgery. Machado de Souza et al[12] presented an abstract examining early postoperative gastric emptying measured by paracetamol absorption following laparoscopic cholecystectomy and found a nonsignificant trend toward higher paracetamol plasma levels among patients who received sugammadex, suggestive of faster gastric emptying.

On the basis of historical studies of muscarinic and anticholinergic combinations and limited evidence on sugammadex, we do not have a clear mechanistic explanation for our observation. The most plausible explanation is that the longer time to first bowel movement in the neostigmine/glycopyrrolate (control) group was secondary to direct effects of these medications on bowel function rather than sugammadex effect. Our secondary analysis, which found that higher ratios of neostigmine to glycopyrrolate were also associated with earlier bowel movements, supports our notion that the earlier time to first bowel movement with sugammadex was because anticholinergic agents were not coadministered with this reversal technique. There are limitations inherent to the retrospective nature of this study. Both known and unknown confounding variables may not have been evenly distributed among patients and thus not accounted for in the analyses. Although we have identified several associations between sugammadex exposure and bowel movement in comparisons with 2 separate populations who had sugammadex reversal with neostigmine and glycopyrrolate, we cannot conclude causality. This association may be a surrogate marker of other unidentified clinical characteristics. Although hospital records were thoroughly reviewed for the time to first bowel movement, some patients may not have accurately reported it, and this study does not account for reporting inaccuracies.

Another important limitation is that our outcome of interest (time to first bowel movement) was reliant on nursing documentation. Further, patients could have had undocumented bowel movements or been discharged home before defecation. Again, we doubt that these factors would bias results because it is implausible that documentation accuracy of postoperative bowel movements on postoperative wards would be influenced by the reversal technique and would be reproducible over 2 time epochs. However, this limitation did preclude us from examining other aspects of gastrointestinal function, such as time to first flatus. Regardless, we emphasize caution in interpretation of our finding and feel it critical to confirm this result with prospective randomized trials.

CONCLUSION

The patients undergoing intraperitoneal surgery who had aminosteroid NMBA reversal with sugammadex had earlier time to first bowel movement than patients who had reversal with neostigmine/glycopyrrolate. This result should be confirmed with prospective trials before widespread adoption into practice protocols designed to enhance various aspects of functional recovery.

ACKNOWLEDGMENTS

Dr Weingarten had complete editorial control over study design, data abstraction, data analysis, and manuscript preparation.

The Mayo Clinic Institutional Review Board approved this study (protocol No. 17-003136, approved April 25, 2017). Consistent with Minnesota Statute 144.295, all patients in this study provided prior authorization for research use of their health records.

The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp, Kenilworth, NJ.

Dr Deljou. acquired and interpreted data and made critical revisions of the work for important intellectual content. Dr Ballinger acquired and interpreted data and made critical revisions of the work for important intellectual content. Dr Schroeder analyzed and interpreted

data and made critical revisions of the work for important intellectual content. Dr Sprung analyzed and interpreted data and made critical revisions of the work for important intellectual content. Dr Weingarten conceived and designed the work, acquired and interpreted data, analyzed and interpreted data, supervised the study, drafted the work, made critical revisions of the work for important intellectual content, and gave final approval of the version to be published. All authors read and approved the final manuscript.

Abbreviations and Acronyms: **HR** = hazard ratio; **IPTW** = inverse probability of treatment weighting; **IQR** = interquartile range; **LOS** = length of stay; **NMBA** = neuromuscular blockade agent

Grant Support: This project was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck Sharp and Dohme. Dr Weingarten had complete editorial control over study design, data abstraction, data analysis, and manuscript preparation.

Potential Competing Interests: Dr Weingarten currently serves as a consultant to Medtronic Inc in the role as chairman of the Clinical Endpoint Committee for the Prodigy Trial; has received research support from Respiratory Motion,Inc (study equipment), and unrestricted investigator-initiated grants from Merck, (active) and Baxter International (completed). The other authors have no conflicts of interest to disclose.

Publication dates: Received for publication March 6, 2019; revisions received May 2, 2019; accepted for publication June 10, 2019.

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*Mayo Clinic does not endorse specific products or services included in this article.

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