



Recent Trends in the Practice of Procedural Sedation Under Local Anesthesia for Catheter Ablation, Gastrointestinal Endoscopy, and Endoscopic Surgery in Japan: A Retrospective Database Study in Clinical Practice from 2012 to 2015

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Abstract

Objectives To investigate changes in sedation practice during 2012–2015, using a large health claims database, for catheter ablation (CA), gastrointestinal endoscopic examination (EE), and surgery (ES) after dexmedetomidine (DEX) was approved for procedural sedation in 2013. We assessed the trends of sedative utilization, sedative-analgesic combinations, and, additionally, incidence of complications from 2012 to 2015.

Methods Using the database provided by Medical Data Vision Co., Ltd. (Tokyo, Japan), annual utilization proportions of the sedatives and sedative-analgesic combinations and occurrence of complications were calculated in patients with a record of local anesthesia and CA, EE, and/or ES but without general anesthesia used on the same day. The sedatives studied were DEX, propofol (PF), midazolam (MDZ), diazepam, flunitrazepam, thiamylal (TIA), thiopental (TIO), and ketamine.

Results DEX was used most often for CA, followed by PF. From 2012 to 2015, the proportion of DEX increased from 30 to 36%, and that of PF slightly decreased from 29 to 27%. The order of utilization proportions did not change for EE or ES. The use of benzodiazepines, particularly MDZ, predominated. The top five sedative-analgesic combination patterns changed during the study period for CA, but not for EE or ES. The most common complications with CA, EE, and ES were bradycardia, nausea and vomiting, and respiratory depression, respectively. There were no changes in the complications' trends for the procedures.

Conclusion The approved use of DEX for procedural sedation resulted in changes for CA, but not for EE or ES. The complication trends did not change.

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Key Points

After the approval of dexmedetomidine for procedural sedation in 2013, utilization of dexmedetomidine increased, widening the gap from the second most used sedative, propofol for catheter ablation; benzodiazepines predominated the sedative utilization for endoscopic examination and surgery without change in the order of utilization proportion.

Sedation practice has changed for catheter ablation after 2013, but not for gastrointestinal endoscopic examination or surgery.

1 Introduction

Sedation is a necessary component of invasive catheter ablation (CA) and gastrointestinal endoscopy performed under local anesthesia. Flunitrazepam (FZP) had been the only agent approved for procedural sedation under local anesthesia in Japan until 2013. Although efficacy and safety profiles vary according to the sedative, most of the available agents entail a risk of respiratory depression [1–4], possibly resulting in fatality [1, 3, 4]. Such a risk could be further exacerbated by co-administration with analgesics during CA and endoscopy.

In 2013, dexmedetomidine (DEX) was approved for an additional indication—i.e., procedural sedation under local anesthesia. DEX, a highly selective α_2 -adrenergic agonist, produces sedation while maintaining the patient's ability to communicate [5, 6] and analgesic and anxiolytic effects [7, 8], with a minimal risk for respiratory depression [9–13]. Simultaneously, however, DEX inhibits sympathetic nervous activities, to cause hypotension and bradycardia; and stimulates α_{2B} -adrenergic receptors in the vascular smooth muscle at high plasma concentrations (e.g., at the initial loading dose) to cause transient hypertension [11, 14, 15].

In Japan, prior to the additional indication for DEX, midazolam (MDZ) and diazepam (DZP) followed by propofol (PF) had been most frequently used for gastrointestinal endoscopy [16] and PF for CA [17]. During 2003–2007, sedative-related events were the most commonly reported complications, with high frequencies of respiratory depression, hypoxia, and apnea [18]. However, updated and comprehensive data covering all the diverse sedatives including the newly added DEX, which would be expected to alter the sedation trend, is still lacking.

Therefore, using a large “real-world” database, this study aimed to investigate changes in sedation practice for CA, gastrointestinal endoscopic examination (EE), and endoscopic surgery (ES) following the approval of an added indication (procedural sedation) for DEX in 2013. We assessed the following trends from 2012 to 2015: (1) sedative utilization; (2) sedative-analgesic combinations; and additionally, (3) incidence of complications.

2 Materials and Methods

This retrospective study used a pre-existing de-identified claims database. The Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to a study exclusively using the de-identified data. Therefore, this study was not obligated to apply for ethical approval by an institutional review board and

informed consent. This article adheres to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) consensus [19].

2.1 Data Source

This study used the health claims database provided by Medical Data Vision Co., Ltd. (Tokyo, Japan). The database collects data from 247 acute-care hospitals distributed across Japan, covering more than 14 million patients as of the end of July 2016. The recorded information includes patient demographic data, diagnosis, prescription of drugs, treatment, and surgery. The database avoids personally identifiable information by de-identifying the data prior to incorporating them in the database.

2.2 Study Sample

We analyzed the data collected from April 2012 to March 2015. We included hospitals whose data were updated monthly for 2 years from April 2012 (92 hospitals). We first identified the procedures conducted with procedural sedation under local anesthesia according to the following criteria: records of (1) local anesthesia (Supplementary Table 1 in the electronic supplementary material (ESM)), and (2) prescription of DEX, PF, or MDZ, but (3) without a record of general anesthesia (Supplementary Table 2 in the ESM) on the same day as local anesthesia. The criteria yielded 1498 codes, 60 of which were identified to be related to CA, EE, or ES (Supplementary Table 3 in the ESM).

Thus, we included patients meeting the following criteria: (1) age ≥ 18 years; (2) recorded height and body weight; (3) use of local anesthesia; (4) having undergone CA, EE, and/or ES (identified with the 60 codes); but (5) no record of general anesthesia on the same day as local anesthesia.

2.3 Definitions

Based on an expert review, we defined the sedatives, analgesics, and complications. The sedatives were DEX, PF, benzodiazepines (MDZ, DZP, FZP), barbiturates (thiamylal (TIA), thiopental (TIO)), and ketamine. Analgesics included fentanyl, remifentanyl, pethidine (PET), morphine, flurbiprofen, buprenorphine, and pentazocine (PTZ). The sedatives and analgesics were identified using prescription records.

Symptoms that are commonly reported during procedural sedation under local anesthesia and that were evaluated as complications in this study were respiratory depression, hypertension, hypotension, tachycardia, bradycardia, and nausea and vomiting. Hypertension and hypotension were excluded from the analysis of CA because prophylactic medications are usually administered for blood pressure fluctuation during the procedure. We operationally defined the

complications using records of drug prescription, medical procedures, and medical devices (e.g., oxygen mask) that are commonly used to counteract the corresponding symptoms (Supplementary Table 4 in the ESM). We counted only the complications that occurred on the same date as CA, EE, or ES, but not those that occurred on the day before. Respiratory depression during EE and ES, however, was counted regardless of its occurrence on the day before the procedure.

2.4 Statistical Analysis

Data were summarized descriptively. Demographic data on the date of the first CA, EE, or ES procedure were summarized as the patient's characteristics.

To evaluate a time trend of sedative utilization, we calculated the proportion of each sedative prescription and each sedative-analgesic combination (including a sedative alone), by procedure (CA, EE, ES), for each fiscal year (i.e., from 1 April to 31 March of the following year), using as the denominator the sum of the procedures, and the prescriptions of all the combinations (including a sedative alone), respectively.

To further understand the sedation trend during 2012–2015, we explored for the proportion of sedative use for each procedure—CA or endoscopy (EE + ES) by sedative. The proportions were calculated by dividing the number of CA or endoscopic procedures by the sum of the prescriptions for each sedative. Because the duration and level of invasiveness may decide the sedatives used for endoscopy, we also calculated the proportion of procedures by site (upper and lower bowel for EE and ES) for each sedative by dividing the number of procedures (i.e., upper- or lower-bowel EE, or upper- or lower-bowel ES) by the total sedative prescriptions for endoscopy.

For analyzing complications, we calculated the annual occurrence of each complication by procedure (CA, EE, ES). In addition, we calculated the occurrence of each complication by the sedative-analgesic combination.

All analyses were conducted using SAS release 9.4 software (SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Demographic Characteristics

Of the 129,439 patients included in this study, 3483, 99,917, and 26,039 patients underwent CA, EE, and ES, respectively (Table 1). The mean (SD) ages of patients were higher for endoscopy than for CA [CA: 63.31 (13.01) vs. EE: 67.69 (14.38) vs. ES: 69.71 (13.47)]. The proportion of men was slightly greater than that of women for all the procedures.

3.2 Time Trend of Sedative Utilization by Procedure

From 2012 to 2015, DEX was most commonly used for CA, followed by PF (Fig. 1a). Although the order of DEX and PF did not change, the proportion of DEX increased from 30 to 36% and that of PF slightly decreased from 29 to 27% to gradually widen the gap between DEX and PF, which had been almost equally used in 2012. The third most commonly used sedative prior to 2014 (TIA) was replaced by TIO in 2015. The other sedatives were rarely or never used (MDZ and DZP < 5%, FZP and ketamine 0%).

The order of utilization proportions did not largely change for EE (Fig. 1b). Benzodiazepines dominated the top three places, accounting for > 90% of the sedative utilization each year. MDZ was used most often throughout the study period (> 50%). The other sedatives, including DEX, were rarely or never used (PF ≤ 1%, others 0%).

The order of utilization proportions did not largely change for ES (Fig. 1c). Benzodiazepines dominated the top three places, accounting for > 90% of the sedative use each year. MDZ was used most often throughout the study period (> 50%). The other sedatives, including DEX, were rarely used for EE, whereas use of PF increased (from 3 to 4% from 2012 to 2015). After 2013, the proportions of DEX and PF slightly increased (DEX from 0 to 2% and PF from 3 to 4% from 2013 to 2015).

3.3 Usage of Each Sedative

Figure 2 indicates the proportion of procedures performed under sedation. DEX was used more often for CA (68.5%) than for endoscopy (31.5%) (Fig. 2a). Of the endoscopic procedures, the proportions of utilization for EE and ES were 17.1 and 82.9%, respectively. Regarding the procedural endoscopic sites, DEX was used the most for ES of the upper bowel (68.5%) (Fig. 2b).

TIA and TIO were also mostly used for CA (CA vs. endoscopy: TIA 99.2 vs. 0.8% and TIO 99.6 vs. 0.4%, respectively) (Fig. 2a).

PF was used more for endoscopy (65.6%) than for CA (34.4%) (Fig. 2a). Of the endoscopic procedures, the proportions of utilization for EE and ES were 45.0 and 55.0%, respectively. Regarding the procedure sites, PF was used the most for ES of the upper bowel (47.3%) (Fig. 2b).

The trend of usage was similar among benzodiazepines (MDZ, DZP, FZP), which were mostly used for endoscopy (CA vs. endoscopy: MDZ 0.1 vs. 99.9%, DZP 0.6 vs. 99.4%, FZP 0 vs. 100%) (Fig. 2a). Of the endoscopic procedures, benzodiazepines were used most often for EE of the upper bowel (MDZ 66.7%, DZP 70.3%, FZP 65.6%) (Fig. 2b).

Endoscopy accounted for most of the procedures without sedation (CA 0.5% and endoscopy 99.5%) (Fig. 2a). Of the

Table 1 Patient demographic characteristics

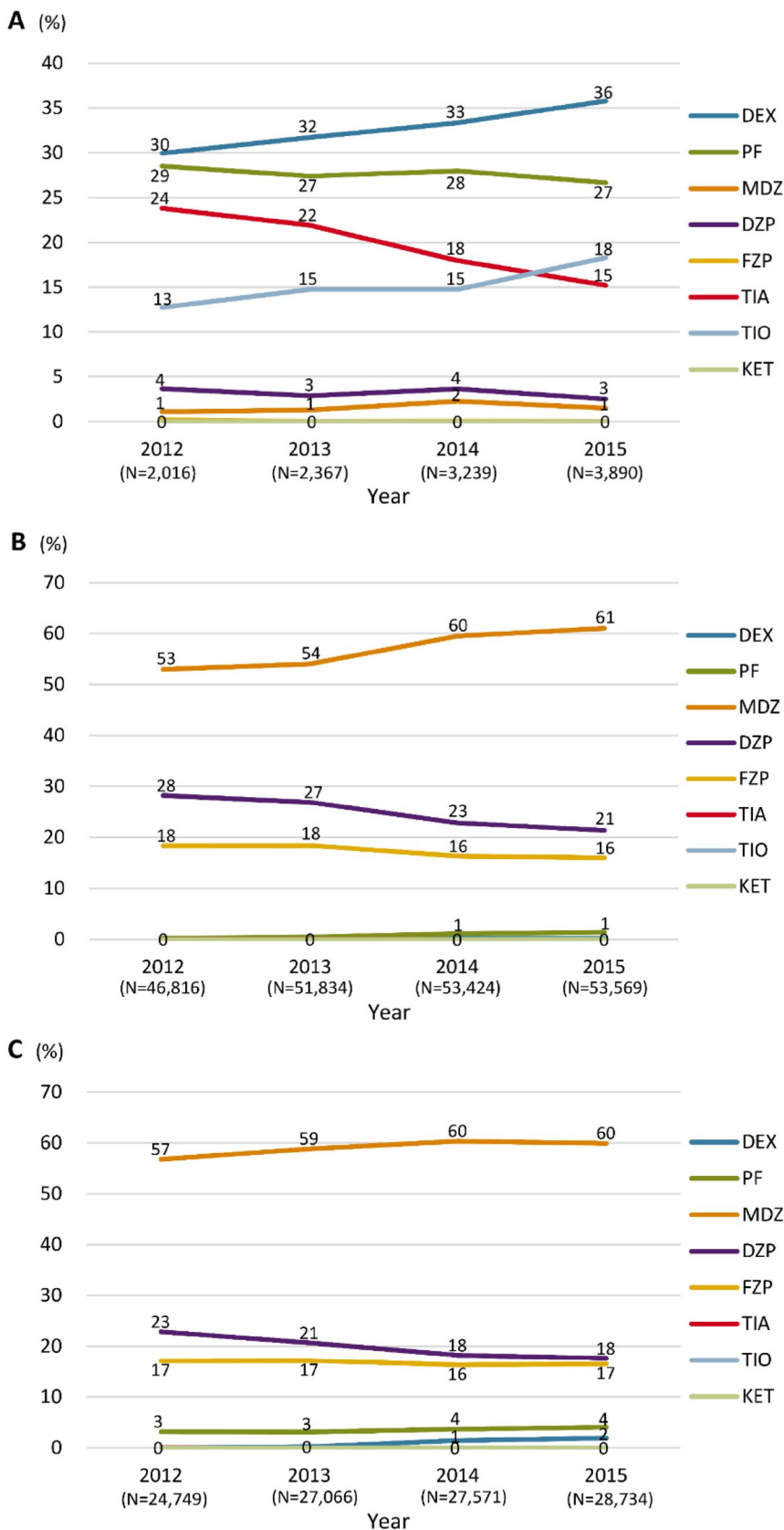
	All	DEX	PF	MDZ	DZP	FZP	TIA	TIO	Ketamine	No sedative
CA										
N	3483	1675	1310	101	150	1	732	835	0	996
Age, years	63.31 ± 13.01	64.94 ± 11.13	64.12 ± 11.41	63.52 ± 11.28	65.10 ± 13.79	69	64.04 ± 11.18	64.60 ± 11.18	–	60.90 ± 15.59
< 65 years	1577 (45.28)	678 (40.48)	557 (42.52)	52 (51.49)	60 (40.00)	0 (0)	309 (42.21)	349 (41.80)	–	522 (52.41)
≥ 65 years	1906 (54.72)	997 (59.52)	753 (57.48)	49 (48.51)	90 (60.00)	1 (100)	423 (57.79)	486 (58.20)	–	474 (47.59)
Sex										
Male	2261 (64.92)	1138 (67.94)	904 (69.01)	71 (70.3)	103 (68.67)	1 (100)	502 (68.58)	594 (71.14)	–	553 (55.52)
Female	1222 (35.08)	537 (32.06)	406 (30.99)	30 (29.70)	47 (31.33)	–	230 (31.42)	241 (28.86)	–	443 (44.48)
EE										
N	99,917	77	512	19,650	7352	5652	1	1	7	67,262
Age, years	67.69 ± 14.38	65.16 ± 13.88	70.24 ± 15.32	66.79 ± 14.82	64.72 ± 14.56	66.87 ± 14.73	69	89	59.86 ± 23.97	68.33 ± 14.14
< 65 years	34,573 (34.60)	33 (42.86)	151 (29.49)	7281 (37.05)	3203 (43.57)	2039 (36.08)	0 (0)	0 (0)	5 (71.43)	22,098 (32.85)
≥ 65 years	65,344 (65.40)	44 (57.14)	361 (70.51)	12,369 (62.95)	4149 (56.43)	3613 (63.92)	1 (100)	1 (100)	2 (28.57)	45,164 (67.15)
Sex										
Male	56,465 (56.51)	55 (71.43)	253 (49.41)	10,358 (52.71)	3822 (51.99)	3131 (55.4)	1 (100)	0 (0)	2 (28.57)	39,181 (58.25)
Female	43,452 (43.49)	22 (28.57)	259 (50.59)	9292 (47.29)	3530 (48.01)	2521 (44.6)	0 (0)	1 (100)	5 (71.43)	28,081 (41.75)
ES										
N	26,039	76	427	9897	3510	2899	1	0	4	9800
Age, years	69.71 ± 13.47	68.26 ± 13.54	70.27 ± 14.45	70.99 ± 13.64	68.96 ± 13.52	70.34 ± 13.46	80	–	71.50 ± 14.62	68.35 ± 13.21
< 65 years	8212 (31.54)	21 (27.63)	127 (29.74)	2752 (27.81)	1204 (34.30)	867 (29.91)	0 (0)	–	2 (50)	3446 (35.16)
≥ 65 years	17,827 (68.46)	55 (72.37)	300 (70.26)	7145 (72.19)	2306 (65.70)	2032 (70.09)	1 (100)	–	2 (50)	6354 (64.84)
Sex										
Male	16,053 (61.65)	53 (69.74)	266 (62.30)	5706 (57.65)	2159 (61.51)	1716 (59.19)	0 (0)	–	3 (75)	6528 (66.61)
Female	9986 (38.35)	23 (30.26)	161 (37.70)	4191 (42.35)	1351 (38.49)	1183 (40.81)	1 (100)	–	1 (25)	3272 (33.39)

Results are given as mean ± SD or number (%)

The table summarizes the data at the date of the first record of either CA, EE, or ES, whichever came earlier, between 2012 and 2015

CA catheter ablation, DEX dexmedetomidine, DZP diazepam, EE endoscopic examination, ES endoscopic surgery, FZP flunitrazepam, MDZ midazolam, PF propofol, SD standard deviation, TIA thiamylal, TIO thiopental

Fig. 1 Time trends for sedative utilization proportions from 2012 to 2015 by procedure. **a** Catheter ablation. **b** Endoscopic examination. **c** Endoscopic surgery. The year was defined as the interval from 1 April to the following 31 March. The proportion of each sedative includes both single and combination use of the sedative. The proportion was calculated using as the denominator the sum of each procedure. *CA* catheter ablation, *DEX* dexmedetomidine, *DZP* diazepam, *EE* endoscopic examination, *ES* endoscopic surgery, *FZP* flunitrazepam, *MDZ* midazolam, *PF* propofol, *SD* standard deviation, *TIA* thiamylal, *TIO* thiopental



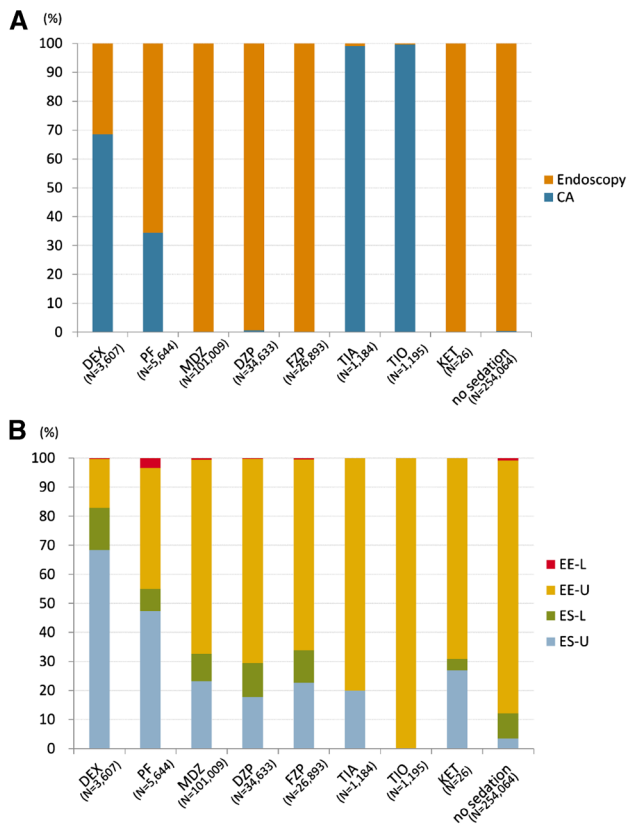


Fig. 2 Proportion of procedures performed under sedation during 2012–2015 by sedative. **a** Catheter ablation vs. endoscopy. **b** Upper- vs. lower-bowel endoscopic examination vs. upper- vs. lower-bowel endoscopic surgery. Endoscopy includes EE and ES. CA catheter ablation, DEX dexmedetomidine, DZP diazepam, EE endoscopic examination, ES endoscopic surgery, FZP flunitrazepam, L lower bowel, U upper bowel, MDZ midazolam, PF propofol, SD standard deviation, TIA thiamylal, TIO thiopental

endoscopic procedures, the proportion was largest for EE of the upper bowel (86.9%) (Fig. 2b).

3.4 Time Trend for Sedative-Analgesic Combinations

Figure 3 displays the top five sedative-analgesic combinations, which accounted for > 10% of all combinations in each year. Combination patterns were more diverse for CA than for endoscopy.

For CA, the top five combinations changed each year, resulting in nine combinations to appear in the end in 2015. The combinations of DEX + PF + TIA + PTZ and PF + TIA + PTZ were used the most during 2012 (15% for each), followed by DEX + TIA + PTZ (10%), DEX + PF + PTZ (8%), and DEX + PF + TIO + PTZ and DEX + PTZ (7%) (Fig. 3a). In 2015, DEX + PF + TIO + PTZ was used the most (15%), followed by PF + TIA + PTZ

(11%), DEX + TIA + PTZ (9%), DEX + PF + PTZ (8%), and DEX (5%). From 2012 to 2015, use of DEX + PF + TIA + PTZ decreased from 15 to 1% and DEX + PF + TIO + PTZ increased from 7 to 15%. Among analgesics, PTZ alone ranked in the top five places.

For endoscopy, the same five combinations ranked among the top five places for use in EE and ES; however, the order of those five differed between the procedures. For EE, MDZ was used the most in 2012 (36%), followed by DZP (24%), FZP (17%), MDZ + PET (12%), and MDZ + PTZ (5%) (Fig. 3b). MDZ was also used the most in 2015 (44%), followed by DZP (19%), FZP (15%), MDZ + PET (11%), and MDZ + PTZ (6%). The order did not change throughout the study period, with MDZ remaining at the top, although the proportion of MDZ increased from 2012 to 2015. For ES, MDZ + PTZ was used the most in 2012 (23%), followed by MDZ (18%), MDZ + PET (13%), DZP (10%), and FZP (9%) (Fig. 3c). MDZ + PTZ was also used the most in 2015 (24%), followed by MDZ (18%), MDZ + PET (15%), DZP (9%), and FZP (8%). The order did not change throughout the study period. Single-sedative administration of DZP and FZP slightly decreased from 2012 to 2015 (DZP: from 10 to 9%, FZP: from 9 to 8%, respectively).

3.5 Time Trend of Complications

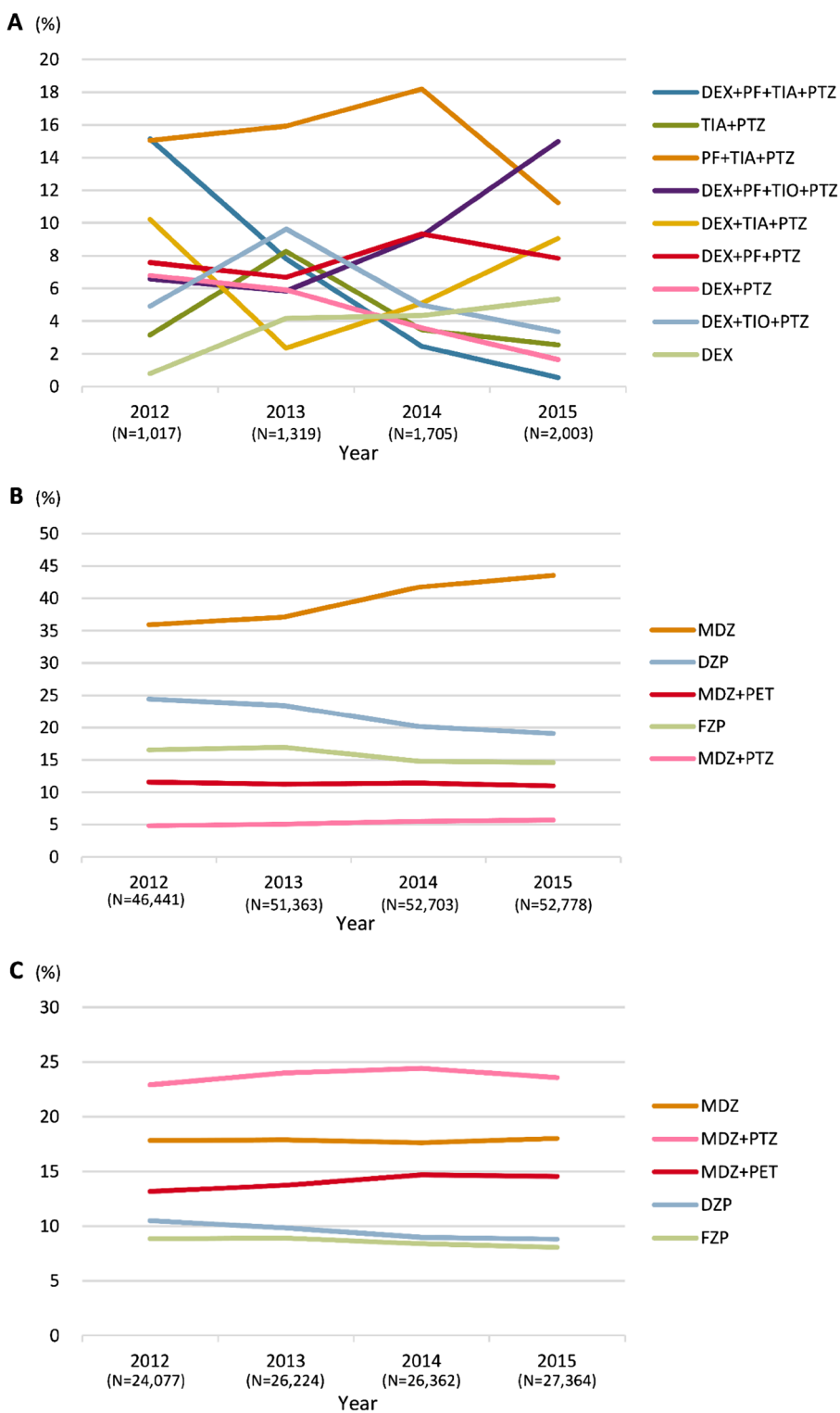
The occurrence of complications did not change throughout the period for any of the procedures (Table 2). In 2015, bradycardia was most commonly observed for CA (63.6%), followed by nausea and vomiting (24.9%), tachycardia (4.5%), and respiratory depression (0.3%). Nausea and vomiting was most commonly observed for EE (45.0%), followed by respiratory depression (8.5%), bradycardia (0.5%), hypotension (0.3%), hypertension (0.1%), and tachycardia (0.0%). Respiratory depression was most commonly observed for ES (26.8%), followed by nausea and vomiting (16.8%), bradycardia (4.6%), hypotension (1.9%), hypertension (0.8%), and tachycardia (0.1%).

3.6 Complications by the Top Five Sedative-Analgesic Combinations

Because there were no changes in trends from 2012 to 2015, we calculated the occurrence of complications by the top five sedative-analgesic combinations only in 2015 (Table 3).

For CA, respiratory depression was not observed in patients receiving the top five sedative-analgesic combinations (Table 3). The occurrence of bradycardia for the utilization including DEX was 77.6% for DEX alone, 74.6% for DEX + TIA + PTZ, 68.7% for DEX + PF + TIO + PTZ, and 51.0% for DEX + PF + PTZ. Bradycardia in patients on utilization not including DEX (i.e., PF + TIA + PTZ) was 25.8%. In less than 10% of patients receiving the top five

Fig. 3 Time trends of sedative-analgesic utilization proportions from 2012 to 2015 by procedure. **a** Catheter ablation. **b** Endoscopic examination. **c** Endoscopic surgery. The figure displays the top five sedative-analgesic combinations, which accounted for more than 10% of all the combinations, including single sedative administration. The year was defined as the interval from 1 April to the following 31 March. The proportion of each combination was calculated using as the denominator the sum of all the combinations. *CA* catheter ablation, *DEX* dexmedetomidine, *DZP* diazepam, *EE* endoscopic examination, *ES* endoscopic surgery, *FZP* flunitrazepam, *MDZ* midazolam, *PET* pethidine, *PF* propofol, *PTZ* pentazocine, *TIA* thiamylal, *TIO* thiopental



combinations, tachycardia was observed. The occurrence of nausea and vomiting was 78.5% for DEX + TIA + PTZ, followed by 42.7% for DEX + PF + TIO + PTZ, 23.6% for PF + TIA + PTZ, 5.6% for DEX, and 4.5% for DEX + PF + PTZ.

For those undergoing EE, the occurrence of respiratory depression in combinations including MDZ was 51.6% for MDZ + PTZ, 35.6% for MDZ + PET, and 24.5% for MDZ (Table 3). For those taking the combinations not including MDZ, respiratory depression was observed in 5.3% for DZP and 4.5% for FZP. Bradycardia was observed by the

Table 2 Occurrences of complications by procedure from 2012 to 2015

	2012	2013	2014	2015
CA				
N	1636	1972	2292	2646
Bradycardia	993 (60.7)	1218 (61.8)	1420 (62.0)	1682 (63.6)
Nausea and vomiting	389 (23.8)	490 (24.8)	558 (24.3)	659 (24.9)
Tachycardia	70 (4.3)	110 (5.6)	131 (5.7)	118 (4.5)
Respiratory depression	9 (0.6)	3 (0.2)	5 (0.2)	7 (0.3)
EE				
N	158,826	165,660	164,095	160,211
Nausea and vomiting	63,298 (39.6)	68,004 (41.1)	70,342 (42.9)	72,090 (45.0)
Respiratory depression	11,853 (7.4)	13,665 (8.2)	14,322 (8.7)	13,676 (8.5)
Bradycardia	1454 (0.9)	1182 (0.7)	815 (0.5)	769 (0.5)
Hypotension	568 (0.4)	667 (0.4)	509 (0.3)	525 (0.3)
Hypertension	244 (0.2)	226 (0.1)	218 (0.1)	168 (0.1)
Tachycardia	19 (0.0)	27 (0.0)	27 (0.0)	23 (0.0)
ES				
N	39,708	42,548	42,317	42,624
Respiratory depression	9686 (24.8)	11,255 (26.5)	11,440 (27.0)	11,422 (26.8)
Nausea and vomiting	7843 (19.8)	7645 (18.0)	7336 (17.3)	7159 (16.8)
Bradycardia	2415 (6.1)	2271 (5.3)	2112 (5.0)	1940 (4.6)
Hypotension	826 (2.0)	1021 (2.4)	846 (2.0)	789 (1.9)
Hypertension	288 (0.7)	273 (0.6)	331 (0.8)	347 (0.8)
Tachycardia	17 (0.0)	13 (0.0)	14 (0.0)	28 (0.1)

Results are given as number (%)

Complications included were respiratory depression, hypertension, hypotension, tachycardia, bradycardia, and nausea and vomiting

For CA, hypertension and hypotension were excluded from the analysis because the prophylactic medications are usually administered for blood pressure fluctuation during the procedure

We operationally defined the complications by the records of drug prescription, medical procedures, and medical devices (e.g., oxygen mask) that are commonly administered to counteract the corresponding symptoms (Supplementary Table 4 in the electronic supplementary material (ESM))

We counted only the complications that occurred on the same date, but not on the day before, of CA, EE, or ES. Respiratory depression during EE and ES, however, were counted, regardless of the occurrence on the previous day of the procedure

CA catheter ablation, EE endoscopic examination, ES endoscopic surgery

Table 3 Occurrences of complications for the top five sedative-analgesic combinations by procedure

Rank	Combination	N	Bradycardia	Nausea and vomiting	Tachycardia	Respiratory depression	Hypertension	Hypotension
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CA								
1	DEX + PF + TIO + PTZ	300	206 (68.7)	128 (42.7)	18 (6.0)	0 (0)	–	–
2	PF + TIA + PTZ	225	58 (25.8)	53 (23.6)	4 (1.8)	0 (0)	–	–
3	DEX + TIA + PTZ	181	135 (74.6)	142 (78.5)	1 (0.6)	0 (0)	–	–
4	DEX + PF + PTZ	157	80 (51.0)	7 (4.5)	2 (1.3)	0 (0)	–	–
5	DEX	107	83 (77.6)	6 (5.6)	9 (8.4)	0 (0)	–	–
EE								
1	MDZ	22,982	78 (0.3)	10,241 (44.6)	3 (0.0)	5635 (24.5)	51 (0.2)	17 (0.1)
2	DZP	10,072	53 (0.5)	5608 (55.7)	2 (0.0)	535 (5.3)	39 (0.4)	5 (0.0)
3	FZP	7707	4 (0.1)	3016 (39.1)	0 (0)	343 (4.5)	9 (0.1)	2 (0.0)
4	MDZ + PET	5797	56 (1.0)	1470 (25.4)	0 (0)	2061 (35.6)	11 (0.2)	3 (0.1)
5	MDZ + PTZ	3016	364 (12.1)	739 (24.5)	0 (0)	1557 (51.6)	38 (1.3)	7 (0.2)
ES								
1	MDZ + PTZ	6454	500 (7.7)	1419 (22.0)	6 (0.1)	3514 (54.4)	295 (4.6)	39 (0.6)
2	MDZ	4929	61 (1.2)	624 (12.7)	2 (0.0)	1900 (38.5)	59 (1.2)	25 (0.5)
3	MDZ + PET	3980	382 (9.6)	537 (13.5)	0 (0)	1935 (48.6)	41 (1.0)	14 (0.4)
4	DZP	2410	195 (8.1)	220 (9.1)	0 (0)	130 (5.4)	16 (0.7)	6 (0.2)
5	FZP	2203	9 (0.4)	345 (15.7)	1 (0.0)	461 (20.9)	11 (0.5)	7 (0.3)

Because the trend of complications did not change from 2012 to 2015, we calculated the occurrence of complications for the top five combinations only in 2015

Complications included were respiratory depression, hypertension, hypotension, tachycardia, bradycardia, and nausea and vomiting

Hypertension and hypotension were excluded from the CA analysis because the medications are usually administered prophylactically for blood pressure fluctuation during the procedure

We operationally defined the complications by the records for drug prescription, medical procedures, and medical devices (e.g., oxygen mask) that are commonly administered to counteract the corresponding symptoms (Supplementary Table 4 in the electronic supplementary material)

We counted only the complications that occurred at the same date, but not on the day before, CA, EE, or ES. Respiratory depression during EE and ES, however, was counted regardless of the occurrence on the previous day of the procedure

CA catheter ablation, DEX dexmedetomidine, DZP diazepam, EE endoscopic examination, ES endoscopic surgery, FZP flunitrazepam, MDZ midazolam, PET pethidine, PF propofol, PTZ pentazocine, SD standard deviation, TIA thiamylal, TIO thiopental

12.1% of the patients receiving MDZ + PTZ but $\leq 1\%$ of those who received other combinations. The occurrence of nausea and vomiting in patients on combinations of sedatives and analgesics was 25.4% for MDZ + PET and 24.5% for MDZ + PTZ. Those with sedatives alone were 55.7% for DZP, 44.6% for MDZ, and 39.1% for FZP. In less than 2% of the patients who received one of the top five combinations, hypertension, hypotension, and tachycardia were observed.

For those undergoing ES, the occurrence of respiratory depression in those with the combinations including MDZ was 54.4% for MDZ + PTZ, 48.6% for MDZ + PET, and 38.5% for MDZ (Table 3). Those with the combinations not including MDZ were 20.9% for FZP and 5.4% for DZP. The occurrence of nausea and vomiting with the combinations of sedatives and analgesics was 22.0% for MDZ + PTZ and 13.5% for MDZ + PET. Those with sedatives alone were 15.7% for FZP, 12.7% for MDZ, and 9.1% for DZP. In less than 10% of the patients who received any of the top five

combinations, bradycardia, tachycardia, hypotension, or hypertension were observed.

4 Discussion

Using a large “real world” database, this study investigated changes in trends of sedation practice and complications after the approval of an additional indication (i.e., procedural sedation) for DEX in 2013. Since 2013, DEX has become more widely used for CA sedation. During endoscopy, contrarily, for which DEX had rarely been used before 2013, the additional indication of DEX did not increase its use even after 2013, although other off-label agents have been continuously used. The trend of complications was not affected for any of the procedures.

DEX and PF were selected for longer and painful procedures, i.e., CA, and for endoscopic procedures, ES rather

than EE, possibly because of their stable level of sedation. The unique profile of DEX, particularly its analgesic effect [7, 15], may have rendered it a desirable option for severely painful CA. DEX may also be beneficial for lengthy endoscopic procedures that induce pain (e.g., endoscopic submucosal dissection (ESD), endoscopic retrograde cholangiopancreatography (ERCP)) [20, 21]. Our further analysis of endoscopic procedures (ESD, ERCP, EMR, and others) indicated a tendency of DEX being used for longer procedures, such as ESD. Specifically, DEX was more frequently used for longer procedures (i.e., ESD: 83.7% (857/1024)) than comparatively shorter procedures (i.e., ERCP: 4.3% (44/1024) and endoscopic mucosal resection (EMR): 1.1% (11/1024)). PF was also mainly used for longer procedures (ESD: 63.7% (2847/4471); ERCP: 20.3% (906/4471); and EMR: 2.3% (101/4471)). For comparison, benzodiazepines (MDZ, DZP, and FZP) were more frequently used for shorter procedures (ERCP: 38.1% (30,004/78,648), 29.4% (8509/28,926), and 37.4% (8232/21,992), respectively; EMR: 18.9% (14,827/78,648), 25.0% (7244/28,926), and 22.1% (4865/21,992), respectively) than longer procedures (ESD: 14.7% (11,584/78,648), 11.5% (3327/28,926), and 12.2% (2693/21,992) among respective benzodiazepines). DEX may be less suitable for short-duration procedures, because DEX takes 15–25 min until reaching the target plasma concentration level [22], resulting in more use in longer procedures.

Benzodiazepines predominated for endoscopic procedures, consistent with previous reports from Japan [16]. Because endoscopic procedures, particularly EE, take only a short time, benzodiazepines, which can be administered as a single injection or infusion, may be preferred, particularly MDZ, which is short acting. The analgesics PTZ (the only analgesic used for CA) and PET were frequently used. PTZ were selected for not being classified as narcotics, unlike ketamine, which was rarely used; while PET, a narcotic, was used possibly because it does not require a narcotic prescription, suppresses the gag reflex [3], and produces a sedative effect.

Barbiturates were used more often for CA than for endoscopy possibly because of the familiarity with their use during defibrillation among cardiologists [23]. Contrarily, barbiturates use among gastroenterologists are perhaps unlikely in daily practice. TIA and TIO have similar profiles, but the order of the use for CA reversed in 2015, which is difficult to explain with the available data.

Without information on adverse events available in the database, we operationally defined the complications using records of treatments generally administered to counteract these symptoms. Thus, treatments administered only for preventative purposes may have partially been included as complications. Irrespective of this compromise, the pattern of complications did not deviate largely from the safety profile

of the sedatives that were commonly used for each procedure. For example, DEX induces sedation by sympatholytic effects through stimulation of α_{2A} -adrenoceptors in the locus ceruleus, resulting in a minimized risk for respiratory depression to a greater extent than other sedatives, including PF [21], MDZ [21, 24], and TIA [25]. By increasing parasympathetic activity, however, DEX induces bradycardia. The frequent utilization of DEX for CA may partly explain the high bradycardia incidence and rare respiratory depression incidence during CA. In contrast, respiratory depression occurred more frequently during EE and ES than during CA possibly because of the predominant MDZ utilization, which increases the risk for respiratory depression [1]. Regardless of the sedative used, the inherent risk of fatal cardiopulmonary depression necessitates close monitoring during sedation [4]. For optimal sedation, understanding each sedative's profile and selecting and/or combining the sedatives and analgesics is vital according to the characteristics of the procedures and patients' conditions.

There are some limitations to this study. First, the results are subject to selection bias as the Medical Data Vision database was derived from the hospital-based claims data obtained only from acute-care hospitals. Therefore, the study population might not represent the general population prescribed with sedation. Second, the database may not cover all of the relevant information (e.g., doses/dosages, monitoring). Nonetheless, with the large sample obtained, this study may depict the overall trend of procedural sedation in Japan. Third, the absence of relevant data may make it difficult to confirm the purpose of the sedative prescription (e.g., as sedative or analgesic), even though we minimized the possibility of using some of the sedatives as an anesthetic by excluding patients who underwent general anesthesia. Lastly, the definitions adopted may not precisely represent the actual utilization or complications. Especially, we operationally defined complications by the records of prescriptions of drugs and medical devices that are commonly administered to counter complications, which may underestimate or overestimate the occurrence of complications. Our definition, however, may allow us to evaluate the occurrence of complications that require medical treatment.

5 Conclusion

We investigated the trends of sedative utilization and complications in clinical practice using a large, “real-world” database. DEX has become more widely used for CA after the approval of the additional indication (procedural sedation). The sedation trend did not change in endoscopic procedures, as the dominant use of benzodiazepines persisted. The trend of complications did not change after 2013.

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Author contribution AM conceived the study. AM, MM, HS, YF, and YI designed the study. AM and MM acquired the data. MM and TL analyzed the data. AM, MM, TL, and YI interpreted the data. AM drafted the manuscript. All authors critically revised the manuscript and approved its final submitted version.

Compliance with Ethical Standards

This retrospective study used a preexisting de-identified claims database. The Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to a study exclusively using the de-identified data. Therefore, this study was not obligated to apply for the ethical approval by institutional review board and informed consent.

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Conflicts of interest AM, MM, HS, and YF are employees of Pfizer Japan, Inc. TL is an employee of Clinical Study Support, Inc. YI declares no conflict of interest.

Data availability Data are purchased from Medical Data Vision, Co., Ltd (MDV, Tokyo, Japan). For inquiries on the dataset analyzed in this study, please contact MDV (<https://www.mdv.co.jp/>).

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