From Microscopic To Endoscopic Transsphenoidal Surgery: A Single Institution's Learning Curve In Pituitary Tumor Treatment

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Abstract

Introduction: Transsphenoidal surgery with an operative microscope was a standard procedure for pituitary adenomas resection in our institution. Still, since the end of 2020, we have shifted the protocol to endoscopic transsphenoidal approach. This paper presented our learning curve in pituitary surgery using endoscopy instruments.

Method: Patients with pituitary tumors who received transsphenoidal surgery during 2019 – 2021 were included. We compared the extent of resection, re-operation rate, blood loss volume, operative time, and complications of postoperative cerebrospinal fluid (CSF) leakage and diabetes insipidus (DI) between microscopic and endoscopic transsphenoidal approaches. Tumors extension to the suprasellar area and cavernous sinus were also analyzed to see their relationship with surgical outcomes.

Result: Twenty-seven (55.1%) and 22 (44.9%) patients underwent microscopic transsphenoidal and endoscopic transsphenoidal surgery. There was no significant difference in total removal rate, re-operation rate, post-operative CSF leakage rate, blood loss volume, and operative time between the two approaches. Patients who received endoscopic surgery had a higher rate of DI ($P = 0.002$). Tumors extension to cavernous sinus was a significant predictor of total resection rate ($P = 0.002$). Multivariate analysis showed that surgical approach, suprasellar and cavernous sinus extension did not significantly affect the extent of surgery.

Conclusion: Our endoscopic and microscopic surgery results are comparable despite the limitation of experience with endoscopy instruments. This report supports our transition from microscopic to endoscopic pituitary surgery.

1. Introduction

As tumors originated from adenohypophysis, pituitary adenomas (PAs) are the third most common intracranial tumors, accounting for 10%-25%.[1] In the most recent report by CBTRUS, the tumors had incidence rate of 17.9% of all primary central nervous system (CNS) tumors by histology.[2] PAs are classified as clinically nonfunctioning pituitary adenomas (NFPAs) or functional pituitary adenomas (FPAs); prolactinomas, adrenocorticotropic hormone (ACTH) secreting, growth hormone (GH) secreting, or thyroid-stimulating hormone (TSH) secreting adenomas are considered as FPAs.[3] According to size, PAs are described as microadenoma if the size is less than 10 mm, while macroadenomas have a size of more than 10 mm.[4]

Suprasellar extension of the tumor could compress the optic chiasm and optic nerve, resulting in visual field defect, mainly bitemporal deficit, and blurred vision. Lateral or cavernous sinus extension could lead to diplopia due to compression of the third, fourth, and sixth cranial nerve, with sixth nerve compression being the most prevalent because of its medial position in cavernous sinus.[5,6] In functional adenoma, the presentations depend on the hormone over secretion. Increased prolactin levels in prolactinoma may result in decreased libido and infertility in both sexes, oligomenorrhea or amenorrhea and galactorrhea in women, and erectile dysfunction in men. Overproduction of growth hormone results in hand and foot enlargement, alterations in facial features, and gigantism if the excessive hormone develops before the epiphyses closing. Hypercortisolism due to ACTH excessive production causes Cushing syndrome, manifested by weight gain, redistribution of fat resulting in centripetal obesity, diabetes mellitus, hypertension, and mood disorders.[4]

Surgery is indicated for patients with visual impairment due to tumor compression and prolactinomas resistant to medical therapy.[7,8] Transsphenoidal approach has been a gold standard for sellar tumor surgery and has evolved significantly over past century.[9] Horsley performed first operation for PAs using transcranial approach,[10] and by 1907, Schloffer was the first to resect pituitary tumor with nasal transsphenoidal approach. Cushing then introduced sublabial transsphenoidal approach in 1910, and in 1960 Hardy developed Cushing's technique with the introduction of microscope.[11] Jankowski et al. demonstrated a fully endoscopic surgery for PAs in 1992, arguing that the approach improved the surgeon's ability to identify vital structures and perform tumor resection with suprasellar and parasellar extension.[12] In recent years, endoscopic transsphenoidal surgery has been a favoured procedure due to its advantages of improved visibility and minimum invasiveness.[13]

Before the availability of endoscopy instruments, our institution used transsphenoidal surgery with an operative microscope was the standard procedure for PAs resection. Since the end of 2020, the surgery has shifted to endoscopic approach to provide surgeons a wider field of view and minimal invasiveness. We have not evaluated our surgical results using the new instruments compared to the old method. This paper presented a retrospective study to report our learning curve in pituitary surgery that had shifted from microscopic to endoscopic approach.

2. Method

2.1 Selection Criteria

A retrospective analysis was conducted following approval from ethical committee of Universitas Indonesia. Patients with sellar tumors who received transsphenoidal surgery in Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, during 2019–2021 were included in our study. Exclusion criteria were tumors with histopathology results of non-pituitary adenoma. All patients underwent clinical examination including visual acuity, visual field, and eye movements. The hormonal analysis and radiological examination of brain magnetic resonance imaging (MRI) were performed to establish the diagnosis.

2.2 Surgical Procedure

Microscopic approach was a standard procedure in our institution for sellar tumor before the end of 2020. Since then, after the availability of endoscopy instruments, all patients with PAs who had been indicated for operation had received endoscopic transsphenoidal surgery as a standard of treatment.

Both surgeries were done under general anesthesia. Consultant neurosurgeons performed microscopic surgery using Zeiss Pentero Microscope through transseptal approach. The head is slightly tilted so that the bridge of the nose is almost kept parallel to the operating chamber and turned fifteen degrees towards the surgeon. The patient, operator, and surgical assistant position are depicted in Fig. 1. The nostrils were decongested using gauze soaked by 1:100,000 epinephrine. Nasal mucosa near columella was incised using a small blade, then the mucosa was bluntly dissected from the septum to find a junction of nasal septum and rostrum of sphenoid. Hardy's speculum was docked to widen the operating field. After dissecting the septum from the rostrum, the keel bone was removed using Pituitary Rongeurs, and the sphenoidal ostium could be identified at 11 and 1 o'clock. Sphenoidotomy was done using chisel and Kerrison Rongeurs to find sphenoidal sinus. Mucosa and septum of sphenoid sinus could be found and removed using Pituitary Rongeurs and forceps. The surgeons identified the sellar floor, clivus posteriorly, planum sphenoidale anteriorly, the bulge of the internal carotid siphon immediately juxtaposed to the sella, and the opticocarotid recess in between the optic nerve and the carotid protuberance. The location of sellar floor was confirmed by fluoroscopy. The sellar floor was opened using a chisel, and dural incision was performed in rectangular or vertical fashion. Under microscope visualization, the tumor removal was performed from the posterior and then anterior parts. The surgeons resected the tumor in a piecemeal fashion using tumor forceps and curette. Hemostasis was done with bipolar cautery and Surgicel absorbable hemostat. If cerebrospinal fluid (CSF) leakage was encountered, packing of sellar floor was performed with fat, fascia lata, and fibrin glue. Nasal tampon was applied at the level of the middle meatus, and the mucosal incision was closed with an absorbable suture. The nasal packing was removed 48 to 96 hours after surgery.

The scrub nurse is positioned on the patient's left side, the surgeon stands on the patient's right side, and the anesthesiologist remains at the patient's feet. An assistant stands to the surgeon's left to direct the endoscope, allowing the primary operator to use bimanual microsurgical technique for tumor resection. The positioning of the patients is similar to the position of the microscopic approach.

We used Karl Storz Endonasal Skull Base instruments for endoscopic transsphenoidal surgery. We used two approaches in the endoscopic endonasal procedure: transostial and transseptal. In transostial approach, after the nasal mucosa was decongested with epinephrine solution, middle turbinate was set aside to ipsilateral under endoscopy guidance to find the sphenoidal ostium medial to the superior turbinate. Sphenoethmoidal recess and surrounding mucosa could be coagulated using monopolar cautery to prevent bleeding, and the mucosa was dissected to expose the sphenoidal ostium. Keel bone was dissected from nasal septum and removed using Pituitary Rongeurs. Sphenoidotomy was done with chisel, and procedure in sphenoidal phase was similar with microscopic but under endoscopic assistance. The surgeons could use single nostril technique if the size of the nose were sufficient to fit the scope and the surgical instruments. If the nostril size was too small, binostril technique could be used. We generally performed four-hand techniques in the sellar phase: the first surgeon using both hands held the instruments to dissect or remove the tumor, while the second surgeon held the endoscope and suction. Binostril technique was used to avoid the tools from colliding with each other. The endoscopic transseptal approach followed the same procedures with microscopic; only the use of endoscopy or microscope made them different.[14,15]

2.3. Outcome Assessment

We evaluated the extent of resection postoperatively, with gross-total removal was defined by no pathological contrast enhancement in head CT immediately (1–2 days) after surgery. CSF leakage was evaluated clinically by the presence of post-nasal drip and rhinorrhoea postoperatively. We routinely observed fluid output and balance of patients who received sellar tumor surgery. The diagnosis of diabetes insipidus (DI) was established if the urinary production was increased (> 1500 mL/8 hour) with the rise of blood sodium level, low urinary sodium value, and diluted urine (< 300 mOsm/kg). Re-operation was performed if the patients did not gain symptoms improvement or their deficit worsened, with MRI evaluation showing large residue or regrowth of the tumor. Length of operation and blood loss volume of both surgeries were collected for our analysis.

2.4 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 25. Categorical data is indicated by the number and percentage, while its mean and standard deviation indicates numerical data. The two groups, namely endoscopic and microscopic, were then compared based on sex, age, total resection, leakage, re-operation, DI, blood loss, and duration of operation using the Chi-Square test or Fisher's exact test for categorical data. Independent samples T-test or Mann-Whitney test were used for numerical data. In addition, multivariate analysis was also carried out using binary logistic regression to assess variables affecting the extent of resection. P-value < 0.05 was considered statistically significant.

3. Result

3.1 Study Characteristic

There were 27 (55.1%) and 22 (44.9%) patients who underwent microscopic transsphenoidal approach and endoscopic transsphenoidal surgery, total of 49 patients, from 2019-2021. Female patients were predominant (51%), with mean age was 47.7. There was no statistical difference between microscopic dan endoscopic approaches regarding patients’ gender and age (P = 0.847 and P = 0.406). Patients who underwent surgery with the endoscopic approach had significantly higher degrees of Knosp than the microscopic approach, with P value of 0.047 (table 1). Eleven (22.4%) patients had functioning pituitary adenoma and thirty-eight (77.6%) patients were nonfunctioning adenoma. Of eleven functioning tumor cases, one patient (9%) had gigantism, and the rest were prolactinoma. The most common manifestations were visual field defect and low vision. Cases with suprasellar extension, defined by Hardy classification of C, D, and E, were 35 patients; cavernous sinus extension, defined by Knosp classification of 2, 3, and 4, was found in 33 patients.

3.2 Outcome Analysis

Gross total removal was achieved in five (18.52%) patients of microscopic approach, and none of the endoscopic surgery patients had total removal. Surgical approach was not a significant factor related to extent of resection, with P value of 0.056 (table 1). Of all cases with suprasellar extension, four (11.43%) had total resection, and only one (7.14%) patient without suprasellar extension achieved gross total tumor removal. No statistical difference was found between tumours with and without suprasellar extension related to total removal (P = 1.00, table 2). Total resection was done in five (31.25%) patients without cavernous sinus extension, and no tumor that had extended to parasella could be removed totally. Cavernous sinus extension was a significant factor to predict tumor total resection (P = 0.002, table 3). In multivariate analysis, surgical approach, suprasellar and cavernous sinus extension did not significantly affect the extent of surgery (table 4).

The re-operation rate was 11.11% in patients who received microscopic surgery and 18.18% in endoscopic cases. All repeated surgeries were performed due to regrowth of the tumor. Of six re-operation cases, one microscopic case was re-operated with endoscopic technique because it was in the transition from microscopic to endoscopic surgery. The correlation between the surgical technique and re-operation rate was not significant (P = 0.685), as shown in table 1. Four (11.43%) patients with suprasellar extension and three (21.43%) cases without suprasellar extension underwent repeated surgery; seven (21.21%) patients with cavernous sinus extension and none of the cases without cavernous sinus extension received re-surgery. Both suprasellar and cavernous sinus extension did not correlated significantly with re-operation rate (P = 0.392 and P = 0.08, table 2 and 3).

3.3 Operative Length and Blood Loss

The mean operative length for microscopic approach was 283.15 minutes, shorter than endoscopic surgery length that was 307.5 minutes, though the difference was not significant (P = 0.193). Microscopic transsphenoidal approach had mean blood loss volume of 130 ml, while mean volume of endoscopic surgery was 146.82 ml. Although the amount of bleeding in endoscopic surgery was higher, the correlation of surgical approach and blood loss was not significant (P = 0.378, table 1).

3.4 Complication Rate

Post-operative CSF leakage was reported in two (7.4%) microscopic cases and two (9.09%) endoscopic patients. Both suprasellar and cavernous sinus extension did not affect the leakage rate (P = 1.00 and P = 0.588). Microscopic and endoscopic surgery did not differ significantly in post-operative CSF leakage risk (P = 1.00), as the leakage rate was 7.4% and 9.09%.

Diabetes insipidus was found in eleven (50%) and two (7.4%) endoscopic and microscopic surgery patients. All patients who met DI insipidus criteria were treated with desmopressin nasal spray or tablet. As shown in table 5, the analysis showed that patients who received microscopic transsphenoidal surgery had significantly lower incidence of DI (P = 0.002) than the endoscopic approach. This study did not track whether the patients had temporary DI or received a long-term desmopressin.

4. Discussion

Several studies have compared outcomes and complications between endoscopic and microscopic endonasal surgery in treating pituitary tumor. Endoscopic approach was reported to have technical superiority of panoramic visualization.[16] Various studies reported several advantages, including superior volume of exposure, improved view of the anatomic structures, less mucosal trauma, shorter hospital stay, decreased blood transfusions, decreased patient discomfort, and improved visual outcomes.[17–21]

Our studies showed that surgical approach did not have significant relation with extent of resection. The result is not in accordance with previous studies that reported endoscopic transsphenoidal surgery significantly increased incidence of gross total removal compared to microscopic surgery.[22–24] However, more studies showed that the endoscopic transsphenoidal approach did not significantly correlate with extent of resection,[21,25–28] similar with our result, though a meta-analysis of 18 papers showed endoscopic approach was superior.[29] Our research also showed that none of the patients who underwent endoscopic surgery had gross total removal, while five of twenty seven patients of microscopic surgery had total tumor resection. Besides higher grade of Knosp in endoscopic patients, this phenomenon could also be explained by the lack of experience in handling endoscopy instruments. Endoscopic transsphenoidal surgery at our institution was first performed in 2020, compared to years of experience of our neurosurgical team in microscopic transsphenoidal surgery. A study by Zaidi et al. showed that microscopic surgeries performed by more experienced neurosurgeons produced more gross total tumor resection than endoscopic surgery. However, the result was not statistically significant.[28]

Besides surgical technique, tumor size and extension should be considered when setting total gross removal as a goal of surgery. Tumors with higher Knosp grade and larger size significantly had lower rate of complete resection, according to a study by Karppinen et al.[25] Those findings are consistent with the result of our research; tumor extension to cavernous sinus was inversely related to gross total resection, while suprasellar extension did not significantly correlate with the extent of resection. The findings are understandable given that the transsphenoidal approach could not reach the lateral side of the sella, and aggressive resection of tumor at cavernous sinus could lead to massive intraoperative bleeding and cranial nerve palsies. It should be noted that endoscopic patients in this study had higher grade of Knosp, but the resection rate was not significantly lower than the microscopic patients'. Suprasellar extension is not a barrier to total resection because it can be resected through an extended endoscopic transsphenoidal approach.[30]

The transsphenoidal approach has offered minimal invasiveness and comparable gross total removal rate than the transcranial approach; however, it has significantly higher rates of CSF leakage complication.[31] Persistent CSF leaking is the major cause of morbidity following transsphenoidal surgery for pituitary tumor.[32] Previous studies' comparison of leakage rates between endoscopic and microscopic transsphenoidal surgery showed different results. In one retrospective study, CSF leakage was significantly higher in endoscopic patients.[33] However, many other papers concluded that surgical approach did not significantly affect the incidence of CSF leakage,[21,22,24–28,34,35] including a meta-analysis of fifteen studies.[13] Our seven months of experience in endoscopic transsphenoidal surgery showed that the post-operative leakage rate was not significantly different from the microscopic approach. It also appeared that tumor extension to suprasellar region or cavernous sinus did not affect the incidence of postoperative leakage. Although the CSF leakage rate was not different, endoscopic surgery is preferable to identify and repair leakage due to its enhanced illumination and visualization. One study reported a high CSF leakage repair success rate with precise confirmation and sufficient exposure of the leakage site using endoscopic transsphenoidal technique.[36]

The rate of DI after surgery was various in previous reports. Some studies reported no significant difference in DI rate between endoscopic and microscopic surgery,[22,24–27,34] while reports by Zaidi et al. and Razak et al. favoured endoscopic over microscopic approach.[28,35] These contrast with a study by Azad et al. that favoured a microscopic approach,[33] consistent with our finding. Unfortunately, our research did not track whether the patients had temporary or permanent DI. With its enhanced visualization, the surgeons may perform more aggressive resections that could lead to stalk manipulation; this phenomenon may explain our result that showed higher incidence of DI in endoscopic patients. However, though the operators tended to be aggressive with an endoscope, the rate of postoperative CSF leakage was not different between the two approaches; this could be elaborated that the intraoperative leakage correction was easier and treated more precisely using endoscopy assistance. This led to successful closure, so clinical CSF leakage did not appear postoperatively.

Several studies reported that endoscopic approach was favourable for shorter hospital stays.[13,34] A meta-analysis by Rotenberg et al. showed that endoscopic patients with fewer hospital stays had less overall surgical duration. The authors suggested the endoscopic surgery was less painful or had less complicated hospital course.[37] However, another meta-analysis by Goudakos et al. reported that, although the result showed significantly shorter hospital stays for endoscopic patients, the difference of operative time and blood loss was not significant.[38] We did not include hospital stay as an outcome variable because it is our hospital protocol for patients who underwent surgery more than 4 hours to receive a minimum five-day course of antibiotics before discharge.

In our study, the endoscopic approach's blood loss and operative length were higher and longer than the microscopic one, although not statistically significant. It appeared that the operator’s skill is an essential factor determining the result. A study by Guo-Dong et al. suggested that duration of surgery affected intraoperative bleeding. Some factors could cause the operative time of endoscopic surgery longer, such as preparation of both nostrils, manipulations that caused bleeding which obscured the lens and required saline irrigation, and inappropriate irrigation.[34] Control of bleeding in the endoscopic approach is challenging, which could prolong surgical time. With years of experience in transsphenoidal surgery using a microscope, it takes time for our neurosurgeons to become accustomed to handling endoscopic instruments effectively. However, the surgical length in our centre gradually declined since the introduction of endoscope to the next seven months, as shown in Figure 2, reflecting our neurosurgical team learning curve.

This study reports our institutional experience in pituitary tumors treatment and evaluates our learning process in handling more sophisticated instruments. We have only used the endoscopy less than a year and already experienced the advantages, such as no need for fluoroscopy intraoperatively and the availability of performing pituitary surgery concomitantly with other microscopic surgery, as our center only have one operating microscope. Several surgical endoscopy workshops and training had been organized to expand our knowledge and sharpen our skills. We believe this report should be continued in the following years after the number of endoscopy surgery is large enough along with improvement of our skills. Our study also showed the outcomes and complications rate between microscopic and endoscopic approach were comparable.

There are some limitations to this study. First, the design of this report is retrospective. Second, we think the number of endoscopic patients in our institution is still small. Third, both microscopic and endoscopic surgeries were performed by different surgeons, so this could introduce outcome bias. Fourth, we did not include clinical outcomes as variables because too few endoscopic patients are available for long-term evaluation.

5. Conclusion

The results of our endoscopic surgery are comparable with the microscopic approach despite our limitation of experience with endoscopy instruments. The decline of operative length in seven months showed the progress of our learning in endoscopic surgery. With its available evidence, this report supports the transition to endoscopic pituitary surgery, and we believe that as our experience increases over time, the result will be more encouraging.

Abbreviations

ACTH, adrenocorticotropic hormone; CNS, central nervous system; CSF, cerebrospinal fluid; DI, diabetes insipidus; FPA, functioning pituitary adenoma; GH, growth hormone; NFPA, nonfunctioning pituitary adenoma; PA, pituitary adenoma; TSH, thyroid-stimulating hormone

Statements & Declarations

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by ethical committee of Universitas Indonesia.

Consent to Participate

The authors have obtained informed consent from individual participants or legal guardians of participants included in the study.

Consent for Publication

Participants or legal guardians of participants have consented regarding publishing their data. The authors also provided informed consent to publish the image in Figure 1.

Availability of Data and Material

The datasets generated in this current study are available from the corresponding author on reasonable request.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Author Contributions

All authors contributed to the study conception and design. RAA and SAHP performed material preparation, YA and RK conducted data collection, and BAW and RWS performed analysis. RAA and SAHP wrote the draft of the manuscript. All authors read and approved the manuscript.

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Tables

Table 1 Study Characteristic and Comparison of Outcome Between Endoscopic and Microscopic Surgery

Parameter		Endoscopic Surgery (N=22)	Microscopic Surgery (N=27)	P value
Gender, male (%)		10 (45,45)	14 (51,85)	0,874*
Age by year (*mean*±SD)		46±14,243	49,07±11,408	0,406**
Knosp Classification (%)	1	3 (13,64)	13 (48,15)	0,047***
	2	4 (18,18)	5 (18,52)	
	3	6 (27,27)	5 (18,52)	
	4	9 (40,91)	4 (14,81)	
Total Removal (%)		0 (0)	5 (18,52)	0,056***
Re-operation (%)		4 (18,18)	3 (11,11)	0,685***
Blood loss in mL (*mean*±SD)		146,82±79,963	130±75,651	0,378****
Operative Length in minute (*mean*±SD)		307,5±63,184	283,15±65,075	0,193***

**Chi-Square Test*, ***Independent-Samples T Test*, ****Fisher's Exact Test*, *****Mann-Whitney Test*, SD – Standard Deviation

Table 2 Comparison Between Tumor with and without Suprasellar Extension Regarding Outcome and Complication

Parameter	With Suprasellar Extension (N=35)	Without Suprasellar Extension (N=14)	P value
Total Removal (%)	4 (11,43)	1 (7,14)	1,000*
Re-operation (%)	4 (11,43)	3 (21,43)	0,392*
Post-operative CSF Leakage (%)	3 (8,57)	1 (7,14)	1,000*
**Fisher's Exact Test*			

Table 3 Comparison Between Tumor with and without Cavernous Sinus Extension Regarding Outcome and Complication

Parameter	With Cavernous Sinus Extension (N=33)	Without Cavernous Sinus Extension (N=16)	P value
Total Removal (%)	0 (0)	5 (31,25)	0,002*
Re-operation (%)	7 (21,21)	0 (0)	0,080*
Post-operative CSF Leakage (%)	2 (6,06)	2 (12,50)	0,588*

**Fisher's Exact Test*

Table 4 *Multivariate Analysis Assessing Variables that Affect the Extent of Resection*

Variables	Total Removal	
	Step	P value
Endoscopic Approach	1	0,998
	2	0,998
Suprasellar Extension	1	0,718
Cavernous Sinus Extension	1	0,997
	2	0,998
	3	0,998

Table 5 Comparison of Complication Between Endoscopic and Microscopic Surgery

Parameter	Endoscopic Surgery (N=22)	Microscopic Surgery (N=27)	P value
Post-operative CSF Leakage (%)	2 (9,09)	2 (7,4)	1,000***
Diabetes insipidus (%)	11 (50)	2 (7,4)	0,002*
**Chi-Square Test*, ***Independent-Samples T Test*, ****Fisher's Exact Test*, *****Mann-Whitney Test*, SD - Standard deviation			

Figures

Figure 1

Endoscopic Transsphenoidal Surgery with an Operator on the Right Side of the Patient, Holding Surgical Instruments, and an Assistant on the Left Side of The Operator, Holding the Endoscope

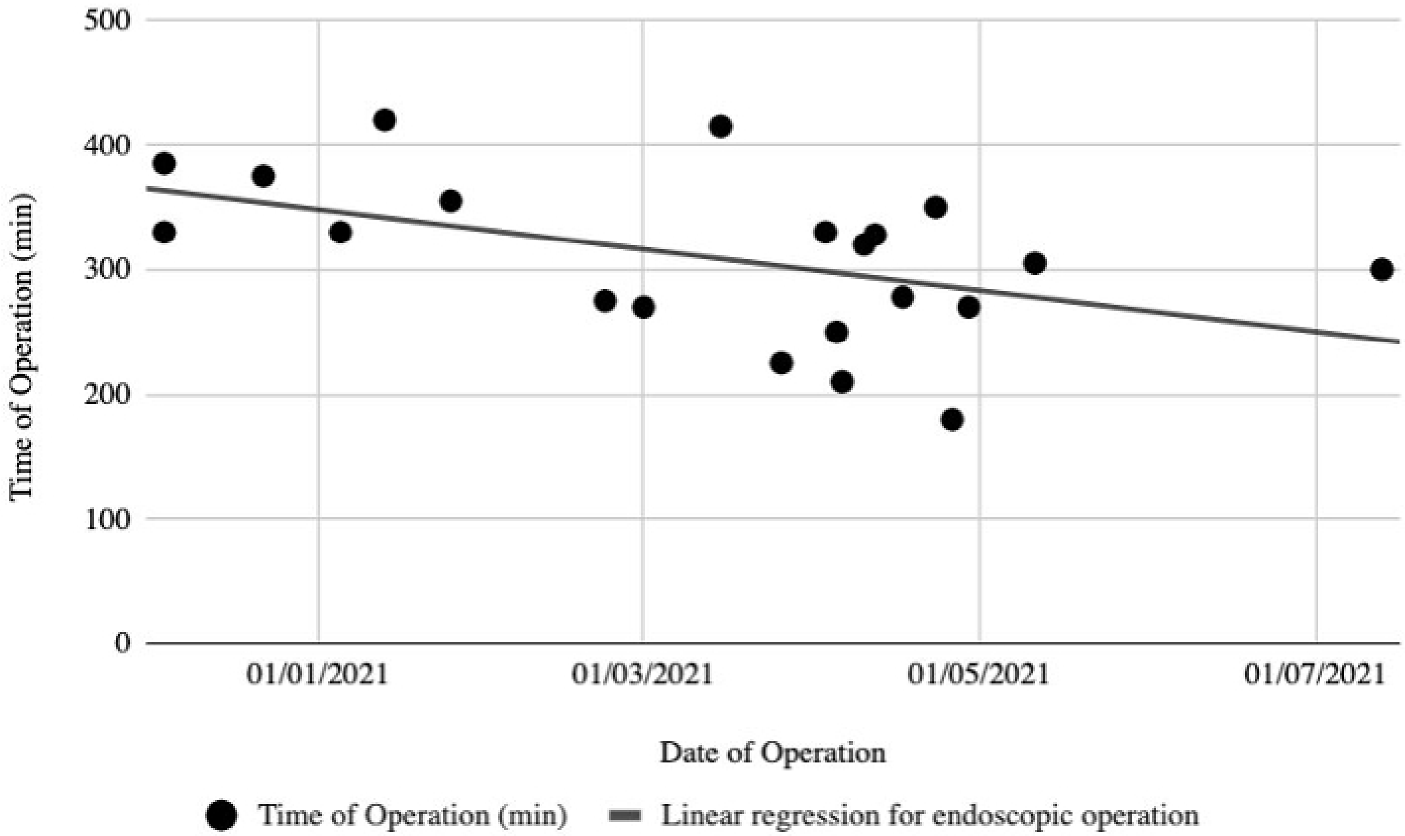

Figure 2

The Change in Duration of Endoscopic Surgery, Showing a Clear Learning Curve from The Introduction of The Endoscope at The End of 2020 to The Mid of 2021