Original Article

Outcomes of the Endoscopic Transsphenoidal Surgery for Resection of Pituitary Adenomas Utilizing Extracapsular Dissection Technique with a Cotton Swab

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Abstract

Purpose: The purpose of this study was to determine the effectiveness and safety of a cotton swab for extracapsular dissection in endoscopic transsphenoidal surgery (ETSS) for pituitary adenoma (PA). **Materials and Methods:** A retrospective review of patients undergoing ETSS for PA from 2014 to 2017 was undertaken. Only patients with extracapsular dissection by cotton swab with the intent to completely remove the tumor were included. Assessment of the prospectively recorded clinical, laboratory, and radiographic presentation as well as the intra- and postoperative data was carried out. Factors influencing the extent of resection were analyzed. **Results:** Of the 222 patients, one hundred cases met the inclusion criteria. The cohort consisted of 81 nonfunctioning and 19 functioning PAs. Fifty patients presented with visual disturbance and 34 patients had prior surgical treatment. The majority of PAs was macroadenoma (97%) with 73% modified Hardy Stage C and 38% Knosp Grade 4. Intraoperative cerebrospinal fluid (CSF) leakage was the most frequently noted complication (78%). Meningitis occurred in three cases and repeat ETSS for CSF leakage repair was necessary in three patients. No death or vascular injury was observed. At 12 months after ETSS, magnetic resonance imaging scan confirmed 43% complete tumor resection. Previous surgery and Knosp Grade 4 were the strong factors for incomplete PA removal by multivariate logistic regression analysis. For functioning PAs, thirteen patients (68.42%) achieved biochemical remission. **Conclusion:** Cotton swab for extracapsular dissection proved its clinical effectiveness and safety. In spite of the technique, negative predictors for complete PA resection were parasellar extension and previous surgery.

Keywords: *Cotton swab, endoscopic, extracapsular dissection, pituitary adenoma, transsphenoidal surgery*

Introduction

Endoscopic transsphenoidal surgery (ETSS) for pituitary adenoma (PA) is one of the most commonly performed procedures in neurosurgery. With gross total PA resection set as the preferred goal, extracapsular dissection is encouraged to identify a tissue plane or cleavage between tumor's pseudocapsule and normal pituitary gland, arachnoid, or diaphragma sellae. Gentle separation of this plane ought to yield complete PA removal while lowering complication rates. Prevedello *et al*. reported, in 2013, the extracapsular dissection technique using a cotton swab.[1] Although it appeared intriguing, clinical outcome by this particular technique does not exist. The primary objective was, first, to evaluate the effectiveness and safety of this technique. The secondary aim was to analyze factors associated with the extent of tumor resection by ETSS.

Materials and Methods

Patient population

The prospectively maintained data of consecutive patients undergoing ETSS for PA from January 2014 to December 2017, performed by the senior author (AH), was reviewed. Only cases with pathology-confirmed PA were included. Each patient's preoperative demographics and clinical presentation were classified based on visual disturbance, endocrinological condition, and prior treatment for PA or asymptomatic presentation.

Surgical technique

All patients underwent ETSS, through binostril access, with the operating surgeons

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standing on their right side. Surgical technique, for the nasal, sphenoidal, and sellar phases, was similar to the previously narrated steps in our earlier publication.[2] Switching from curettage for PA removal, the senior author (AH) utilized cotton swab since 2014, as described by Prevedello *et al*.,[1] for extracapsular dissection [Figure 1]. The intraoperative data, including suspected or definite residual PA, and complication(s) were recorded. For cerebrospinal fluid (CSF) leakage, grading was based on Esposito *et al*.[3] The method for sellar defect repair, depending on CSF leak grade, was similar to our previous literature.[2] Although the cotton swab technique was undertaken in all of the cases, patients who had internal debulking only without circumferential pseudocapsule resection, as their intended surgical goal, were excluded from our analysis.

Pre- and post-operative assessment

For patients with visual disturbance, their visual acuity (VA) and visual field (VF) were assessed using Snellen chart and automated Humphrey perimetry, respectively. The visual function would be examined again, using the same methods, after ETSS at 6-month interval. When compared to preoperative data, the VA and VF outcomes were classified into improved, stable, or worse.

Regarding endocrinological status, preoperative pituitary hormone panel was obtained in every patient. Each hormone was classified as hyperproduction (in functioning PAs), normal, or deficiency. After ETSS, the hormone profiles were examined during the hospital stay and again, at 3-month interval. Functioning PA was considered in remission when the current standard criteria were met after surgery.[4-6] Any new postoperative hormonal deficit, with or without postoperative hormone replacement therapy, was documented.

Preoperative radiographic, computerized tomography and/or magnetic resonance imaging (MRI) scan, features

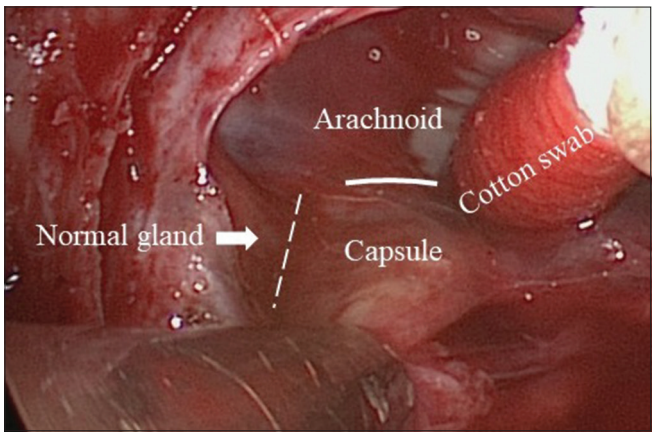

Figure 1: Endoscopic image shows utilizing a cotton swab for extracapsular dissection. The plane between overlying arachnoid and the pseudocapsule (capsule) of the tumor (solid curve line) was established along with the plane separating tumor and the normal pituitary gland (dotted line)

were grouped based on sphenoid pneumatization[7] and modified Hardy's classification.[8] For parasellar extension of the tumor, modified Knosp grading was applied to coronal view evaluation.[9] Enclosed (Knosp 0, 1, 2) versus invasive adenoma (Knosp 3, 4) were categorized. From MRI scan at 12-month after ETSS, complete resection versus residual tumor was determined. For PA volume, each patient's pre- and post-operative MRI scans were calculated by drawing of the region of interest with OsirixLite software (Pixmeo Sarl, Bernex, Switzerland). The percentage of tumor resection was obtained by the pre- minus postoperative volume and divided by preoperative volume.

Postoperative in-hospital complications, such as apoplexy or CSF leakage requiring surgical repair, were noted. After hospital discharge, included patients must have had at least 1 year of follow-up with postoperative MRI scan, endocrinological, and visual assessment. Numerical data would be presented as mean (standard deviation) or median (interquartile range) where appropriate. Utilizing STATA statistical software version 14.2 (StataCorp, College Station, Texas, USA), logistic regression analysis was applied to identify positive and negative predictors, for the extent of resection and CSF leakage, of ETSS. $P < 0.05$ was considered statistically significant.

Results

Of the 222 consecutive cases during the study period, forty patients with non-PA were excluded from our assessment. Another 72 patients had only internal debulking for decompression. Their surgeries were without the initial aim to completely remove the tumor due to the giant size of PA. Hence, those cases were not included. Ten other patients with inadequate data and/or follow-up were omitted, leaving 100 cases for our examination. The median follow-up time was 18.26 months (12.76, 35.16).

Patient demographics, clinical presentation, and preoperative radiographic features [Table 1]

The mean age of patients was 50.41 years old (13.96) with equal proportion of both genders. Among the 50 patients with visual disturbance, forty of them (80%) had abnormal VA, whereas 46 (92%) had VF defect. Eighty-one patients (81%) had nonfunctioning PA. Nineteen functioning PAs (19%) were eight growth hormone-producing, five adrenocorticotropic hormone-producing, four prolactinomas, and two mixed hormone-producing adenomas. There were eight patients (8%) who presented with pituitary apoplexy. The median duration of symptom, in these symptomatic patients, was 12 months (3.24). Nineteen cases (19%) were recurrent Pas, whereas 14 patients (14%) had residual tumors without notable enlargement. Of the 34 patients who underwent pituitary surgery before our ETSS, they had an average of one prior procedure (range 1–5 procedures). Three patients had radiation therapy after multiple surgeries.

Table 1: Patient demographics, clinical presentation and preoperative radiographic features (*n*=100)

Age, year (SD)	50.41 (13.96)
Sex	
Male:female (%)	50:50
Presenting symptoms (%)	
Visual disturbance	50
Ophthalmoplegia	6
Apoplexy	8
Recurrent tumor with growth	19
Residual tumor without growth	14
Asymptomatic	19
Prior treatment (%)	
Surgery	34
Radiotherapy	3
Nonfunctioning pituitary adenoma (%)	81
Functioning pituitary adenoma (%)	19
GH-producing	8
ACTH-producing	5
Prolactinoma	4
Mixed hormone-producing	2
Hormone status, normal: deficit (%)	34:66
Preoperative radiographic features	
Sphenoid pneumatization, sellar:presellar type (%)	73:27
Macroadenoma: Microadenoma (%)	97:3
Median tumor volume, milliliter (IQR)	5.35 (2.7, 10.15)
Normal pituitary gland position (%) (right: midline:left)	44:13:43
Modified Hardy's classification (%)	
Stage 0	1
Stage A	6
Stage B	20
Stage C	73
Modified Knosp grading (%)	
Enclosed adenoma	15
Grade 0	0
Grade 1	1
Grade 2	14
Invasive adenoma	85
Grade 3A	30
Grade 3B	17
Grade 4	38

ACTH – Adrenocorticotropic hormone; GH – Growth hormone; IQR – Interquartile range, SD – Standard deviation

Roughly two-thirds of the cohort had at least one, or more, the axis of the preoperative hormonal deficit.

Most of the PAs were macroadenomas (97%) with the median preoperative volume of 5.35 ml (2.7, 10.15). The majority of tumors were sizeable, having 73% Hardy stage C and 85% invasive adenoma. There was no difference in right-sided (44%) versus left-sided (43%) position of the normal pituitary gland. Sellar-type sphenoid pneumatization was found in 73%.

Intraoperative findings and short-term complications [Table 2]

During ETSS, definite residual PAs were observed in 56 patients. Six cases had suspected tumor remaining. There was no internal carotid artery injury, but the majority (78%) had intraoperative CSF leakage, with Grade 1 being the most common. For short-term complications, postoperative CSF leakage, requiring repeat endoscopic endonasal repair, occurred in one patient with Grade 2 and two patients with Grade 3 intraoperative leakage. Three patients developed meningitis (3%). One of the three ensued from postoperative CSF leakage, whereas the other two patients did not have postoperative leakage.

Logistic regression analysis of risk factors associated with intraoperative CSF leakage, shown in Table 3, demonstrates that modified Hardy stage A was the only protective factor against intraoperative CSF leakage (P = 0.013). Although the increasing age of patients seemed to be influential from univariate analysis (P = 0.028), this factor almost reached statistical significance by multivariate assessment (P = 0.058). Other nonsignificant factors were gender, pre- or postoperative tumor volume, sphenoid pneumatization, modified Knosp grade, intraoperative residual tumor, and complete tumor removal.

As for postoperative CSF leakage requiring ETSS for repair and meningitis, grade 1 intraoperative CSF leakage was the only protective factor against these complications (P = 0.040) [Table 4]. Age, gender, pre- or postoperative tumor volume, sphenoid pneumatization, modified Hardy stage, Knosp grade, intraoperative residual tumor, and complete tumor removal were nonsignificant elements.

Postoperative long-term outcomes

Extent of resection

Comparing preoperative to 12-month postoperative MRI scans, 43 cases had total tumor removal, whereas 57 cases had residual PAs. For all ETSS, the median postoperative volume was 0.2 ml (0, 1.33). The mean percentage of tumor's volume removal was 83.87% (23.52).

From the logistic regression analysis, Knosp 4 (P = 0.007) and history of previous surgery (P < 0.001) were the strong negative factors, in multivariate evaluation, for achieving total tumor removal [Table 5]. Although preoperative tumor volume (P = 0.022) and nonfunctioning PA (P = 0.017) were negative factors in univariate evaluation, they did not reach a significant level by multivariate assessment. Other factors, such as age, gender, modified Hardy stage, or intraoperative CSF leakage, were insignificant.

Visual outcomes

From the 50 patients who presented with visual symptoms, after ETSS, VA improved in 72%, whereas 26% remained stable. VF defect improved in 69% and was unchanged in

29%. One patient, who had prior multiple surgeries and radiotherapy, suffered worsening of her VA and VF after ETSS. All six patients with preoperative ophthalmoplegia improved after surgery.

Hormonal outcomes

At the last follow-up (minimum of 1 year) post-ETSS, remission of functioning PAs was achieved in 13 of 19 patients (68.42%). The majority of patients (67%) had unchanged postoperative hormonal status while 11% incurred, one or more axis, new deficit.

Table 2: Intraoperative data and complications (*n*=100)

Intraoperative residual tumor (%)	62
Definite	56
Suspected	6
Intraoperative CSF leakage (%)	
No leakage	22
Evidence of leakage	78
Grade 1	54
Grade 2	14
Grade 3	10
Internal carotid artery injury (%)	0
Postoperative complications (%)	
Pituitary apoplexy	0
Persistent CSF leakage requiring surgical repair	3
Meningitis	3
Death	0

CSF – Cerebrospinal fluid

Table 3: Factors for intraoperative cerebrospinal fluid leakage

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Increasing age	0.96 (0.92-0.99)	0.028	0.96 (0.91-1.001)	0.058*
Modified Hardy Stage A	0.12 (0.02-0.70)	0.018	0.06 (0.01-0.56)	0.013*

*Logistic regression analysis. CI – Confidence interval; OR – Odds ratio

Table 4: Factors for postoperative cerebrospinal fluid leakage and meningitis

Variable	OR (95% CI)	*P*
Grade 1 intraoperative leakage	0.09 (0.01-0.90)	0.040*

*Logistic regression analysis. CI – Confidence interval; OR – Odds ratio

Discussion

ETSS for PA is becoming the standard of care.[10-13] When possible, extracapsular dissection should be implemented for effectiveness and safety. Prevedello *et al*. proposed the utilization of a cotton swab for this particular maneuver.[1] Abandoning the ring curettes for tumor resection that the senior author (AH) had employed since 2006,[2] the Prevedello's technique was adopted, for extracapsular dissection, from 2014 until present. Despite many years of the very publication, clinical data to support its value still does not exist. We believe this study is the first to report clinical and radiographic outcomes of the cotton swab technique.

Our results confirmed that cotton swab for extracapsular dissection of PA was effective as shown by the remission rate for functioning PA at 68.4%, comparable to previous reports.[14-19] Regarding its safety, there was no life-threatening complication. One patient (2%) with prior extensive treatments did suffer worsening of her vision. Postoperative CSF leakage and meningitis were 3%. These rates were in line with previously reported series for postoperative CSF leakage at 1.4%–16.9%[13,20-24] and meningitis at 0%–10%.[3,13,23]

Rather disappointing was the rate of complete tumor removal at 43%, below the reported range from literature at 62.4% to 90%.[13,20,25-32] Yet, given our intraoperative observation of 62, combined definite and suspected, residual PAs, this was not unexpected. From the logistic regression analysis in Table 5, Knosp 4 proved to be the negative factor for total PA removal. This concurred with our intraoperative finding that most of the remaining tumors were in the cavernous sinus. In addition, previous surgery was also an unfavorable factor for achieving total tumor removal, similarly to reports by others.[13,33] This outcome might, indeed, reflect the fact that our cases were made up of large or postsurgical PAs as tertiary care center would have received from other hospitals. Another likely explanation, for the below-average total PA resection rate, could be that the senior author (AH) frequently exercised caution, by less aggressive tumor resection, for fear of higher grade CSF leakage. Thin pseudocapsules, with marked arachnoid adherence, were not removed in many older, unlike younger, patients for this very reason. The result from the logistic regression analysis in Table 3 reiterated this bias from the surgeon. In addition, having mostly nonfunctioning PAs could have an impact

Table 5: Factors associated with total tumor removal

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Knosp 4	0.21 (0.08-0.52)	0.001	0.20 (0.07-0.65)	0.007*
Preoperative tumor volume	0.92 (0.86-0.99)	0.022	0.98 (0.91-1.06)	0.636*
Previous surgery versus no surgery	0.13 (0.04-0.37)	< 0.001	0.12 (0.04-0.38)	<0.001*
Nonfunctioning versus functioning PA	0.27 (0.09-0.79)	0.017	0.65 (0.18-2.29)	0.500*

*Logistic regression analysis. CI – Confidence interval; PA – Pituitary adenoma; OR – Odds ratio

for the less vigorous resection than those with functioning PAs. It could have potentially caused our lower rate of total tumor removal. This influence was also evident by univariate analysis in Table 5.

Our study limitations are as followed. Despite prospectively collected data, the retrospective analysis yielded lower power of evidence. The second pitfall could be the high percentage of difficult PAs, i.e., previous surgery or invasive adenomas. They had a significant impact on the outcomes regardless of surgical technique. Moreover, the selection bias by the operating surgeon could have affected the total PA resection as aforementioned. In spite of some imperfect results, extracapsular dissection technique using a cotton swab proved its safety and effectiveness.

Conclusion

The outcomes of ETSS by cotton swab technique for extracapsular dissection demonstrated its effectiveness and safety. It should be increasingly utilized by more surgeons for widespread practice. Again, confirmed by our study, previous surgery and Knosp 4 were negative factors for achieving total tumor removal.

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Conflicts of interest

There are no conflicts of interest.

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