Intraoperative calculus or hemorrhage in transurethral seminal vesiculoscopy as a risk factor for recurrent hemospermia

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

We summarized our experience regarding Transurethral Seminal Vesiculoscopy (TUSV) and analyzed both recurrence status and risk factors for recurrence. From January 2010 to December 2020, 48 patients with intractable hemospermia received successful TUSV at Taichung Invalids General Hospital. For the intraoperative findings, the five-year Disease-free Survival rates (DFS) were 74.1% in the no calculus group compared to 37.1% in the calculus group with a significant difference (log-rank $p = 0.015$), 75.0% in the no hemorrhage or no blood clot group compared to 43.2% in the hemorrhage or blood clot group with significant difference (log-rank $p = 0.032$).

Univariate analysis showed intraoperative calculus ($p = 0.040$; HR: 2.94, 95% CI: 1.05–8.21) to be significantly associated with recurrence ($p < 0.05$). Patients with intractable hemospermia who were diagnosed with stones or blood clots found during TUSV experienced a higher rate of hemospermia recurrence.
Introduction

Hemospermia, hematospermia, or haematospermia is defined as blood appearance in the semen. [1] The symptom usually resolves spontaneously in most cases. The mechanisms surrounding the occurrence of hemospermia can be inflammation, infection, lithiasis, cyst formation, obstruction, tumor, vascular related, trauma, iatrogenic related and systemic origin. Recommended imaging studies include Transrectal Ultrasound (TRUS), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI). [2] TRUS is less expensive and less diagnostic than the other tests, but is more commonly used as a diagnostic tool. [3, 4]

Through advancements in endoscopy technology, in vivo Transurethral Seminal Vesiculoscopy (TUSV) was first introduced in 2002. [5] Subsequently, TUSV has been used as a diagnostic and treatment procedure for recurrent hemospermia, persistent hemospermia and intractable hemospermia, with symptoms persisting over 3 months regardless of medical treatment. [6-11] TUSV also has a higher diagnostic rate than TRUS. [3]

The recurrence rate after TUSV treatment has been mentioned to be in a range from 3.4% to 11.76%. [6-11] To the best of our knowledge, there are currently no studies investigating recurrence after TUSV. In this study, we sorted through 48 successful cases and analyzed their recurrence status and risk factors for recurrence.
**Materials and Methods**

**Patients**

This study enrolled patients who had intractable hemospermia and received successful TUSV treatment during the period from January 2010 to December 2020 in Taichung Veterans General Hospital, Taiwan, Republic of China. The diagnosis of hemospermia relied on photos of semen which patients took after sexual activity. The enrolled patients took serum Prostate-specific Antigen (PSA), coagulation tests and TRUS.

For the treatment of hemospermia, an empiric antibiotic ciprofloxacin, 400 mg every 12 hours per os (PO), was administered for at least 2 weeks. For patients with intractable hemospermia who were willing to undergo surgery to relieve symptoms, we provided TUSV.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was granted by the ethics committee of Taichung Veterans General Hospital, Taiwan, Republic of China. The institutional review board number was CE22060A.

**Surgical techniques**

Each patient received either general anesthesia or spinal anesthesia and was placed in the lithotomy position. A semi-rigid ureteroscope (6/7.5-Fr; Olympus, Tokyo, Japan) was inserted into the urethra and introduced to the verumontanum. The bilateral seminal vesicles were then entered through the ejaculation duct or fenestrated from the utricle. Intraoperative manifestations, such as Calculus, hemorrhage, mucosal lesion, were recorded. Seminal vesicle fluid would then be collected for a culture exam. Calculus removal or a biopsy would be performed.
depending on intraoperative manifestations. After the procedure, 10ml normal saline with 80mg
gentamycin irrigation into the seminal vesicle would then be done. [9]

**Statistical analysis**

Numeric variables are expressed as medians (interquartile ranges) and subsequently
compared using the Chi-square test, with significance set at \( p < 0.05 \). Continuous variables are
presented as medians (ranges) and compared using the Mann-Whitney U test, with significance
also set at \( p < 0.05 \). Rates of Disease-free Survival (DFS) up to January 2022 were calculated using
the Kaplan-Meier life table method and compared across groups using the log-rank test.

Differences with \( p \) values < 0.05 were regarded as statistically significant. Univariate and
multivariate analysis utilizing Cox proportional hazard ratios were derived for the outcomes of
interest. All \( p \) values < 0.05 were considered significant in univariate analysis and thus included in
multivariate analyses.
Result

Forty-eight (48) patients diagnosed with intractable hemospermia who underwent successful TUSV were studied. All patients achieved remission. Sixteen (16) patients (33.3%) underwent recurrence up until January 2022. The characteristics between recurrence and non-recurrence are shown in Table 1. In TURS findings, 22 non-recurrent patients (68.8%) experienced overall calculus, while 13 recurrent patients (86.7%) had overall calculus. Eight non-recurrent patients (25%) had Seminal Vesicle (SV) or ejaculation duct calculus, while 2 recurrent patients (13.3%) had SV or ejaculation duct calculus. The median time of follow-up was 39.4 months in the non-recurrent group and 49.8 months in the recurrent group. Complications such as epididymitis occurred in only 2 cases in the non-recurrent group. The median follow-up period was 40.1 months (range, 0.95–134.5 months).
Table 1. Characteristics of patients between recurrence and non-recurrence.

|                                | Total (n=48) | Non-recurrence (n=32) | Recurrence (n=16) | p value |
|--------------------------------|--------------|------------------------|-------------------|---------|
| Age                            | 54.5 (48.3-63.8) | 53.5 (38.3-58.8) | 0.330             |
| Duration (months)              | 12.0 (4.0-23.3) | 13.0 (6.0-24.0) | 0.676             |
| Diabetes mellitus              | 2 (6.3%)     | 1 (6.3%)              | 1.000             |
| Hypertension                   | 6 (18.8%)    | 4 (25.0%)             | 0.712             |
| Previous urinary tract infection | 2 (6.3%)     | 1 (6.3%)              | 1.000             |
| Urolithiasis history           | 5 (15.6%)    | 1 (6.3%)              | 0.648             |
| Erectile dysfunction           | 4 (12.5%)    | 1 (6.3%)              | 0.652             |
| Sexually transmitted disease   | 1 (3.1%)     | 0 (0.0%)              | 1.000             |
| Anti-platelet agent            | 2 (6.3%)     | 3 (20.0%)             | 0.309             |
| PSA                            | 1.1 (0.6-1.4) | 1.0 (0.7-1.7) | 0.803             |
| Digital rectal examination     |              |                       |                   |
| Elastic consistency            | 32 (100%)    | 16 (100%)             | --                |
| Hard consistency               | 0 (0%)       | 0 (0%)                | --                |
| TRUS findings                  |              |                       |                   |
| Overall calcification          | 22 (68.8%)   | 13 (86.7%)            | 0.288             |
| Prostate calculus              | 19 (59.4%)   | 13 (86.7%)            | 0.094             |
| SV or ejaculation duct calculus | 8 (25.0%)    | 2 (13.3%)             | 0.465             |
| Post operative complication    |              |                       |                   |
| Epididymitis                   | 2 (6.3%)     | 0 (0.0%)              | 0.546             |
| Perineal pain                  | 0 (0.0%)     | 0 (0.0%)              | --                |
| Follow-up period (months)      | 39.4 (1.6-66.1) | 49.8 (20.9-96.7) | 0.120             |
| Time to remission (weeks)      | 4.0 (3.0-4.0) | 4.0 (4.0-7.75) | 0.097             |

Chi-square test or Mann-Whitney U test, Median (IQR). *p<0.05, **p<0.01
Numeric variables expressed as medians (interquartile ranges)
Seminal vesicle (SV)
Intraoperative findings

Intraoperative findings of TUSV between the recurrence and non-recurrence groups are shown in Table 2. Overall calculus was found in the utricle or SV in 10 non-recurrent patients (31.3%) and 9 recurrent patients (56.3%). Hemorrhage was found in the utricle or SV in 11 non-recurrent patients (34.4%) and 10 recurrent patients (62.5%).

**Table 2. Intraoperative findings of TUSV between recurrence and non-recurrence.**

| Intraoperative findings     | Total (n=48) | Non-recurrence (n=32) | Recurrence (n=16) | p value |
|-----------------------------|-------------|-----------------------|-------------------|---------|
| Overall calculus            | 10 (31.3%)  | 9 (56.3%)             |                   | 0.175   |
| Utricle                     | 10 (31.3%)  | 7 (43.8%)             |                   | 0.594   |
| Left SV                     | 3 (10.0%)   | 4 (26.7%)             |                   | 0.199   |
| Right SV                    | 2 (6.9%)    | 1 (6.3%)              |                   | 1.000   |
| Hemorrhage or blood clot    | 11 (34.4%)  | 10 (62.5%)            |                   | 0.123   |
| Utricle                     | 2 (6.3%)    | 0 (0.0%)              |                   | 0.546   |
| Left SV                     | 6 (20.7%)   | 7 (46.7%)             |                   | 0.092   |
| Right SV                    | 4 (14.3%)   | 5 (31.3%)             |                   | 0.250   |

Chi-square test. *p<0.05, **p<0.01

Seminal vesicle (SV)

Disease free survival

Regarding the TRUS findings, five-year Disease-free Survival (DFS) rates were 75.0% in the no calculus group compared to 59.0% in the overall calculus group, with the Kaplan–Meier survival curves represented in Fig 1 (log-rank \( p = 0.273 \)). The five-year DFS rates were 54.5% in the no SV or ejaculation duct calculus group compared to 100.0% in the SV or ejaculation duct calculus group, with the Kaplan–Meier survival curves represented in Fig 2 (log-rank \( p = 0.227 \)). In this study, the five-year DFS rates taken from the TRUS findings were insignificantly different.
Fig 1. Kaplan–Meier curves of the disease-free survival rates by TRUS findings of overall calcification. No calcification compared to overall calcification.

Fig 2. Kaplan–Meier curves of the disease-free survival rates by TRUS findings of SV or ejaculation duct stone. No Seminal vesicle (SV) or ejaculation duct calculus compared to SV or ejaculation duct calculus.

For the intraoperative findings, the five-year DFS rates were 74.1% in the no calculus group compared to 37.1% in the calculus group, with the Kaplan–Meier survival curves represented in Fig 3 (log-rank $p = 0.015$). The five-year DFS rates were 75.0% in the no hemorrhage or blood clot group compared to 43.2% in the hemorrhage or blood clot group, with the Kaplan–Meier survival curves represented in Fig 4 (log-rank $p = 0.032$). The five-year DFS rates were 73.7% in the negative intraoperative finding group compared to 47.7% in the positive intraoperative finding group, with the Kaplan–Meier survival curves represented in Fig 5 (log-rank $p = 0.093$). In this study, the five-year DFS rates were significant higher in the intraoperative no calculus group when compared to the calculus group, and in the no hemorrhage or blood clot group when compared to the hemorrhage or blood clot group. The five-year DFS rate was insignificant but trending upward in intraoperative negative findings when compared to positive findings.

Fig 3. Kaplan–Meier curves of the disease-free survival rates by intraoperative findings of calculus. No calculus compared to overall calculus.

Fig 4. Kaplan–Meier curves of the disease-free survival rates by intraoperative findings of hemorrhage or blood clot. No hemorrhage or blood clot compared to hemorrhage or blood clot.
Fig 5. Kaplan–Meier curves of the disease-free survival rates by intraoperative findings. Negative intraoperative finding compared to positive intraoperative finding.

Univariate analysis showed intraoperative calculus ($p = 0.040; \text{HR}: 2.94, 95\% \text{CI}: 1.05–8.21$) to be significantly associated with recurrence, and intraoperative hemorrhage or blood clot ($p = 0.068; \text{HR}: 2.63, 95\% \text{CI}: 0.93–7.43$) to be insignificant but trending upward with recurrence.

Multivariate Cox proportional hazard analysis showed intraoperative calculus ($p = 0.051; \text{HR}: 2.80, 95\% \text{CI}: 1.00–7.90$) to be insignificant but trending upward with recurrence.

**Discussion**

**Effectiveness of preoperative imaging**

TRUS has been mentioned in other studies as having a lower diagnostic yield for hemospermia.

[3] In this study, preoperative TRUS provided a low SV or ejaculatory duct stone detection. TUSV provides better diagnostic rates than a TRUS exam alone. This result is consistent with previous research findings. In this study, TRUS results showed no significant difference in DFS. TRUS findings also failed to provide an association with recurrence prediction. Although TRUS is relatively less invasive and carries less cost, the diagnostic significance and benefit of TRUS in patients with persistent hemospermia requires additional follow-up studies.
Recurrence and hypothesis of hemospermia

The recurrence rate after TUSV treatment is mentioned as being in the range of 3.4% to 11.76%. Amongst the 48 patients in this study, 16 had recurrent hemospermia, with the recurrence rate being 33.33%, which was higher than other studies. However, the median follow-up time in our study was 40.1 months, while the follow-up time in other studies was 5-24 months. Compared with the previous study performed in our hospital, the follow-up time was 12 months, with 4 of 34 patients experiencing recurrence at a rate of 11.76%. Our patients were more regionalized so follow-up at the same hospital was easier. The high recurrence rate may be related to the long follow-up time.

In our study, recurrence-free survival from intraoperative detected stones, hemorrhages, or blood clot was significantly lower when compared with the undetected group. The current hypothesis is that the occurrence of hemospermia, calculus, strictures and inflammation is a vicious cycle. According to that hypothesis, TUSV could interrupt the vicious cycle in addition to providing a diagnosis. For patients with negative intraoperative findings, we believe that TUSV can block the vicious cycle of stricture and inflammation, thus resulting in symptom relief with low recurrence rates. Inflammation may be worse in patients experiencing stones, hemorrhage, or blood clots as detected by TUSV. Fortunately, TUSV can still stop the vicious cycle and relieve symptoms. Because the inflammation is more severe, the possibility of hemospermia recurrence will also increase.
**Success rate**

The success rate of TUSV treatment, as mentioned in the relevant literature, ranges from 90.9% to 96.53%.[8, 9, 11] In this study, 51 patients underwent TUSV, while 6 of them received second TUSV due to recurrent hemospermia. Among the total 57 TUSV treatments, 54 of which were successfully performed. Such a success rate of 94.7% is comparable with the studies reported in the relevant literature. The 3 patients whose TUSV failed all received MRI exams. It turned out that one of them had a seminal vesicle cyst, while the other 2 patients had small prostate cysts. These structural abnormalities may affect the orientation of the ejaculatory ducts or the location of the seminal vesicles, thereby affecting the success rate of TUSV.

**Safety considerations**

Perineal pain, retrograde ejaculation, epididymitis, prolonged hematuria, rectal injury and urinary incontinence are known complications of TUSV. [9, 14] Only 2 patients in this study had postoperative complication of epididymitis. After antibiotic treatment, the infection in these 2 patients was eventually controlled and resolved. Some studies have raised concerns that disruption of normal structures by TUSV could lead to infertility. [14] In recent studies, endoscopic treatments including both TUSV and Transurethral Ejaculation Duct resection (TURED) have shown positive results in the treatment of infertility. [10, 15-18] Real-time TRUS-guided TUSV has also been reported as being a safe procedure that helps avoid rectal injury. [19] Therefore, this study provides strong evidence for the safety of TUSV.
Limitations and future prospects

The present study is retrospective and with a rather small sample size. Further prospective studies with more patients involved would provide more convincing reference and therefore stronger evidence. Besides the aforementioned limitations, the condition of patients with hemospermia usually improves spontaneously without any aggressive treatment. Furuya et al. reported that the spontaneously resolved rate of hemospermia is as high as 88.9%. [19] It is possible that at the time of analysis, this natural process, i.e. hemospermia being relieved spontaneously, had, to a certain extent, contributed to the excellent remission rate after TUSV as well as complicated the assumed cause-and-effect relationship between TUSV and the remission of hemospermia.

Conclusion

As analyzed and concluded in this present study, intraoperative findings can help assess the risk of recurrent hemospermia. Specifically speaking, stones or blood clots found during TUSV for patients with intractable hemospermia contribute to a higher rate of recurrent hemospermia.

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References

1. Kumar, P., S. Kapoor, and V. Nargund, *Haematospermia - a systematic review*. Ann R Coll Surg Engl, 2006. 88(4): p. 339-42.

2. Suh, Y., et al., *Etiologic classification, evaluation, and management of hematospermia*. Transl Androl Urol, 2017. 6(5): p. 959-972.

3. Xing, C., et al., *Prospective trial comparing transrectal ultrasonography and transurethral seminal vesiculoscopy for persistent hematospermia*. Int J Urol, 2012. 19(5): p. 437-42.

4. Han, H., et al., *Magnetic resonance imaging compared to ultrasound as the preferred method for diagnosing intractable haematospermia*. Andrologia, 2021. 53(6): p. e14054.

5. Yang, S.C., et al., *Transutricular seminal vesiculoscopy*. J Endourol, 2002. 16(6): p. 343-5.

6. Han, W.K., et al., *Transutricular seminal vesiculoscopy in hematospermia: technical considerations and outcomes*. Urology, 2009. 73(6): p. 1377-82.

7. Kang, P.M., et al., *Transutricular seminal vesiculoscopy in the management of symptomatic midline cyst of the prostate*. World J Urol, 2016. 34(7): p. 985-92.

8. Chen, R., et al., *Transurethral seminal vesiculoscopy for recurrent hemospermia: experience from 419 cases*. Asian J Androl, 2018. 20(5): p. 438-441.

9. Hu, J.C. and C.S. Chen, *Transurethral seminal vesiculoscopy acts as a therapeutic investigation for intractable hemospermia: Step-by-step illustrations and single-surgeon experience*. Int J Urol, 2018. 25(6): p. 589-595.

10. Liao, L.G., et al., *Etiology of 305 cases of refractory hematospermia and therapeutic options*.
by emerging endoscopic technology. Sci Rep, 2019. 9(1): p. 5018.

11. Chen, W.K., et al., Transurethral seminal vesiculoscopy for intractable hematospermia: experience from 144 patients. BMC Urol, 2021. 21(1): p. 48.

12. Ren, Z.J., et al., Transurethral resection of ejaculatory duct combined with seminal vesiculoscopy for management of persistent or recurrent hemospermia in men with ejaculatory duct obstruction. BMC Urol, 2020. 20(1): p. 34.

13. Furuya, S., N. Masumori, and A. Takayanagi, Natural history of hematospermia in 189 Japanese men. Int J Urol, 2016. 23(11): p. 934-940.

14. Pang, K., B.Z. Dong, and C.H. Han, Commentary on "Transurethral seminal vesiculoscopy for recurrent hemospermia: experience from 419 cases". Asian J Androl, 2020. 22(2): p. 227-228.

15. Dong, Q., et al., [Minimally invasive surgery for ejaculatory duct obstruction in infertile men]. Zhonghua Nan Ke Xue, 2016. 22(4): p. 291-3.

16. Tang, S.X., H.L. Zhou, and Y.L. Ding, [Effectiveness of transurethral seminal vesiculoscopy in the treatment of persistent hematospermia, and oligoasthenozoospermia and azoospermia from ejaculatory duct obstruction]. Zhonghua Yi Xue Za Zhi, 2016. 96(36): p. 2872-2875.

17. Lira, F.T.N., et al., Management of Ejaculatory Duct Obstruction by Seminal Vesciculoscopy: Case Report and Literature Review. JBRA Assist Reprod, 2020. 24(3): p. 382-386.

18. Wang, H.B., et al., [Transurethral seminal vesiculoscopy in treatment of oligoasthenozoospermia secondary incomplete ejaculatory duct obstruction: A report of 8
16 cases]. Beijing Da Xue Xue Bao Yi Xue Ban, 2020. 52(4): p. 642-645.

19. Wang, X.S., et al., Real-time transrectal ultrasound-guided seminal vesiculoscopy for the treatment of patients with persistent hematospermia: A single-center, prospective, observational study. Asian J Androl, 2020. 22(5): p. 507-512.

Supporting information

S1 File. Raw data. File containing data of TUSV follow-up, TRUS findings, Intraoperative findings and recurrence.
Fig 1. Kaplan–Meier curves of the disease-free survival rates by T1.
Fig 2. Kaplan–Meier curves of the disease-free survival rates by T
Fig3. Kaplan–Meier curves of the disease-free survival rates by in
Fig 4. Kaplan–Meier curves of the disease-free survival rates by in...
Fig5. Kaplan–Meier curves of the disease-free survival rates by intraoperative finding. 

- Negative intraoperative finding
- Positive intraoperative finding

\[ p = 0.093 \]