



## Electroejaculation in 12-Year-Old Oncology Patient Prior to Gonadotoxic Chemotherapy: A Case Report and Literature Review

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### Introduction

Advances in cancer therapy have resulted in an increase in the number of long term cancer survivors worldwide. In recent years, average survivals of childhood cancer were reported to be 70-75% in Singapore [1,2]. However, long-term quality of life and side effects of chemotherapy remain pressing issues in survivors. One of the main concerns from chemotherapy is the gonadotoxic effects and subsequent long-term infertility issue following treatment particularly in males. This is especially important as literature has shown that many parents and cancer patients are keen to preserve their fertility [3-5] and hence they should be counseled regarding cryopreservation options prior to initiation of possibly gonadotoxic oncology treatment [6,7]. However, in practice, while oncologists have a positive attitude towards fertility preservation, actual referral rates remains low [8,9].

The primary reason for such low referral rates may be due to the belief that young boys may have difficulty in producing semen. Nonetheless, various methods of spermatozoa extraction such as electroejaculation, Testicular Spermatozoa Aspiration (TESA) or Testicular Spermatozoa Extraction (TESE) may be considered in pediatric oncology patients if they are unable to produce sperm via masturbation. Electroejaculation is less invasive, has few reported side effects (e.g. minimal autonomic dysreflexia and mild rectal mucosal change) [10] and has shown high success rates in sperm extraction [11].

Moreover, in young boys, it may be difficult to ascertain if spermatogenesis has begun. Young age, physical examination findings and biochemical markers may mislead clinicians leading to referrals being deferred because of assumptions that spermatogenesis has not started. However, Hagenas et al. [12] showed that regardless of their age, adolescent boys with testicular volumes of more than 5 ml should be offered semen banking prior to gonadotoxic treatment as 82.5% (71/86) of these patients had spermatozoa obtained successfully for freezing. Bahadur [13] and Menon [14] have similar findings of high success rate in semen cryopreservation in 86.1% (205/238) and 88.5% (138/156) respectively. Subsequent studies have also shown that frozen sperm obtained via sperm extraction has been used successfully in subsequent assisted reproductive techniques [15,16].

### Case Presentation

Osteosarcoma is the eighth most common pediatric cancer with a 5 year overall survival rate of 68% [17]. Chemotherapy has been shown to be useful in treatment of osteosarcoma [18]. However, delayed effects of chemotherapy for osteosarcoma included permanent sterility

and infertility [19] and high rates of oligospermia and azoospermia [20]. We report a case of successful spermatozoa extraction using electroejaculation and TESA in a young 12.3 year old boy prior to initiation of chemotherapy for osteosarcoma. To the best of our knowledge, this case is one of the youngest reported cases of successful spermatozoa extraction via electroejaculation and TESA in literature and is the first case in Singapore. Through this case report, we hope to raise awareness of cryopreservation options among paediatric oncology patients and their family and serve as a guide for further studies on when to offer less invasive cryopreservative options in young boys.

The patient was a 12.3 year old Chinese boy who underwent endoscopic partial resection of low grade intranasal osteosarcoma. The treatment of low grade osteosarcoma consists mainly of surgery. However, the location of the intranasal tumor made local control very difficult, and hence it was decided to initiate a trial of chemotherapy consisting of Ifosfamide and Doxorubicin. Side effects of these chemotherapy drugs include that of gonadal dysfunction and infertility which may sometimes be permanent [21-23]. Prior to initiating chemotherapy, we discussed possibility of long-term infertility issues resulting from gonadotoxic side effects of treatment with the parents and they were keen for cryopreservation.

At the time of diagnosis, physical examination showed Tanner's P2 and G3 with testicular volume of 7.6 cm<sup>3</sup> on each side. Hormonal profile of the boy showed low serum testosterone (0.8 nmol/L), FSH (0.61 U/L) and LH (0.29 IU/L). He was unable to produce semen sample for cryopreservation by masturbation due to his young age. Subsequently, the patient underwent electroejaculation and TESA under general anesthesia. Semen was obtained via 3 methods, namely electroejaculation, retrograde urine sample and TESA.

Intra-operatively, patient was put under general anesthesia and bladder catheterization was done. A digital rectal examination was performed prior to electroejaculation to ensure correct probe size and no compromise of rectal mucosa. Probe was inserted per-rectally with patient in the lateral position. A series of electrical stimulation was administered in a pulsatile manner in the region of the prostate and seminal vesicles until ejaculation occurred. Following the procedure, rectal mucosa is re-examined to assess for any changes. The patient's bladder is catheterized again and bladder flushed with medium until fluid is clear. Motile spermatozoa were obtained from the samples obtained via electroejaculation and retrograde ejaculate in the urine.

TESA was then performed under the same anesthesia to obtain maximal volume of semen for analysis and cryopreservation as

intraoperative semen analysis of electroejaculation appeared to yield little motile sperm at the time of collection.

For TESA, the testis are held firmly to ensure posterior position of the epididymis, and a small caliber needle connected to a syringe is introduced to the anterior surface of the testis to a depth of 1-2 cm. The catheter is then inserted and withdrawn repeatedly. When fluid or testicular tissue is identified, the needle is removed with continuous suction applied. The patient tolerated the procedure well and no side effects were reported.

Testicular tissue retrieved are transferred to a dish containing warm HEPES intra-operatively by embryologists and examined under a high power microscope to assess for presence of sperm. The tissues are cryopreserved and a small amount set aside to assess survivability post-thaw. Number of vials cryopreserved and cryoprotectant used were determined by embryologists in our institution with recommendations to maximize number of vials cryopreserved if possible.

Since only a few motile spermatozoa are needed for assisted reproductive techniques (e.g. In-vitro fertilization), we deemed the semen sample as adequate for cryopreservation due to the presence of motile spermatozoa (Table 1).

| Sample Source        | Density                    | Presence of spermatozoa | Motility |
|----------------------|----------------------------|-------------------------|----------|
| Electroejaculation   | <0.2 x 10 <sup>6</sup> /ml | Occasional spermatozoa  | Motile   |
| TESA                 | <0.2 x 10 <sup>6</sup> /ml | Occasional spermatozoa  | Immotile |
| Retrograde ejaculate | <0.2 x 10 <sup>6</sup> /ml | Occasional spermatozoa  | Motile   |

Table 1: Post-thaw semen analysis.

## Literature Review

Literature review was performed on Pubmed, Google Scholar with key terms 'Electroejaculation', 'young cancers', 'cryopreservation', and 'fertility preservation'. The main purpose of this literature review was to identify other cases of successful electroejaculation prior to chemotherapy in adolescent boys, and to find out the success rate of sperm extraction in these cases, and to identify any significant physical or biochemical factors predictive of successful sperm extraction using electroejaculation.

A total of 6 other studies reporting electroejaculation and cryopreservation in adolescent boys prior to gonadotoxic chemotherapy were identified (Table 2).

## Discussion

Based on our case report and literature review, electroejaculation appears to be a relatively safe procedure for sperm extraction and cryopreservation in adolescent boys who may be unable to masturbate. Success rate of electroejaculation varies between the studies, but generally appears to be around 60%. In these other studies, repeated electrostimulation and TESE (testicular extraction of sperm) were the main options offered to patients who were unable to obtain sufficient levels of sperm.

| Author                   | Study Design | Number and % of patients with successful sperm extraction via EEJ | Age Group            | Youngest Age with successful sperm extraction using EEJ | Factors measured  |
|--------------------------|--------------|---|----------------------|---|---|
| Berookhim BM et al. [11] | Case Series  | 12/28 (60%)   | 11-19 (16.2 ± 2.6)   | 12.7  | 1) Testicular volume (Mean=14.1 ± 3.7 mL)<br>2) Testosterone level (Mean=308 ± 199 ng/dL)<br>3) Serum FSH level (Mean=9.6 ± 10.5 mU/mL)   |
| Hagens I et al. [12]     | Case Series  | 6/12 (50%)  | 12.7-15.8            | 12.9  | 1.) Tanner's staging<br>2.) Testicular volume (8-20 mL)<br>3.) Serum FSH level (0.01-3.33 IU/L)<br>4.) Serum LH level (0.01-4.9 IU/L)<br>5.) Testosterone level (0.01-42.43 nmol/L) |
| Hovav et al. [24]        | Case Series  | 4/6 (66%)   | 15-22 (18 ± 3)       | 15  | -   |
| Adank et al. [25]        | Case Series  | 3/11 (27%)  | 12.6-16.0            | 12.6  | 1.) Tanner's staging<br>2.) Testicular volume (Mean=9.5 mL)   |
| Schmiegelow et al. [26]  | Case Reports | 2   | 14-15                | 14  | 1.) Tanner's staging<br>2.) Testicular volume (Mean=20 mL)  |
| Gat et al. [27]          | Case Series  | 30/45 (66%)   | 13-17 (14.96 ± 1.84) | 13  | 1.) Tanner's staging  |
| Müller et al. [28]       | Case Reports | 2/3 (66%)   | 13 and 14            | 13  | -   |
| Overall                  |              | 52/95 (54.75%, mean excluding case reports)                       | 11-22 (range)        | 13.4 (mean)   |   |

Table 2: Case series and reports of sperm extraction using electroejaculation.

In our patient, electroejaculation was chosen for spermatozoa extraction from this patient due to young age of the patient who was unable to masturbate.

We believe that electroejaculation should also be considered as an option in young patients who are unable to masturbate in view of its less invasive nature and therefore less traumatizing with few risks and complications. If electroejaculation is insufficient to yield satisfactory volume or density of motile sperm for cryopreservation, more invasive methods such as TESA or TESE may be considered.

Based on our literature review, testicular volume appears to be the only factor indicative of successful semen collection [12]. While Tanner's staging, age, hormonal levels and may be indicators of puberty; they have not been found to be definite predictive factors of successful spermatozoa extraction or preservation. This could be limited by the small number of existing data as well as the lack of consistency in the factors that individual centers record in these case studies. We suggest that future large cohort studies take into account age, Tanner's staging, testicular size, serum testosterone and FSH/LH levels in the identification of patients who may be suitable for electroejaculation, and to identify factors predictive of spermatogenesis. More studies may also be conducted on the long-term result on using sperm extracted via electroejaculation from young cancer patients for fertility preservation.

## Conclusion

We present the case of successful spermatozoa retrieval from a young 12.3-year-old paediatric patient. To the best of our knowledge, this is one of youngest reported successful spermatozoa extraction via electroejaculation and TESA in literature and the first case in Singapore and the region.

In our experience, electroejaculation was superior to TESA in spermatozoa retrieval in this paediatric oncology patient with retrieval of more motile sperm. Therefore, electroejaculation may be considered as a first line in young paediatric patients who may be unable to masturbate, before more invasive methods of TESE are considered. Future studies with larger populations should be performed to investigate the factors predicting success rate of sperm retrieval via electroejaculation, as well as documented healthy births from thawed sperm samples obtained in these ways. We also hope to raise awareness among paediatric oncology patients, their parents and physicians managing these patients to the availability of these fertility-preserving options so that more patients may benefit in the future.

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