

The Importance of Cryopreserved Parathyroid Tissue Autotransplantation in the Hypoparathyroidism Treatment after Secondary Hyperparathyroidism Surgery

Sekonder Hiperparatiroidi Cerrahisi Sonrasında Gelişen Hipoparatiroidinin Tedavisinde Dondurularak Saklanan Paratiroid Dokularının Ototransplantasyonunun Önemi

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ABSTRACT

Introduction: Severe hypocalcemia is a rare but serious complication of secondary hyperparathyroidism (SH) surgery. Continuous intravenous calcium replacement is required and patients are not discharged. Cryopreserved parathyroid autotransplantation (CPA) is the most effective and lasting treatment option for severe hypocalcemia. However, a cryopreservation laboratory is necessary for this procedure.

Methods: Subtotal parathyroidectomy performed 150 SH cases (age range: 26-69 years, mean age: 39.5 years, men/women: 2/1) were retrospectively evaluated. Severe hypocalcemia (serum calcium level of <6.5 mg/dL) was developed in 7 (4.6%) cases. CPA was performed and cases were observed in a minimum of 18 months.

Results: After transplantation in five cases, intravenous and oral calcium replacement was ceased and cases were discharged. Transplantation failed in two cases, thus second time CPA. After the second CPA, intravenous calcium is ceased and cases were discharged. Any side effects or complications were not seen during the observation period.

Conclusion: CPA is the most effective and lasting treatment option for severe hypocalcemia. CPA is not difficult to perform but a cryopreservation laboratory and experienced laboratory team are necessary for this procedure. The presence of this laboratory in SH surgery performed centers reduces the risk of mortality and morbidity.

Keywords: Cryopreservation, parathyroid, severe hypoparathyroidism, autotransplantation

ÖZ

Amaç: Şiddetli hipokalsemi, sekonder hiperparatiroidizm (SH) cerrahisinin nadir fakat ciddi bir komplikasyondur. Sürekli intravenöz kalsiyum replasmanı gerekebilir ve hastalar hastaneden taburcu edilemez hale gelebilir. Dondurularak saklanmış paratiroid dokusunun ototransplantasyonu, şiddetli hipokalsemi için en etkili ve kalıcı tedavi seçeneğidir. Ancak bu işlem için kriyoprezervasyon laboratuvarı gerekebilir.

Yöntemler: Subtotal paratiroidektomi yapılan 150 SH olgusu (yaş aralığı: 26-69, ortalama yaş: 39,5, erkek/kadın: 2/1) retrospektif olarak değerlendirildi. Yedi (%4,6) olguda şiddetli hipokalsemi (serum kalsiyum düzeyi <6,5 mg/dL) gelişti. Bu olgulara dondurularak saklanmış paratiroid dokusunun ototransplantasyonu yapılmış ve olgular en az 18 ay gözlemlenmiştir.

Bulgular: Beş hasta transplantasyon sonrası intravenöz ve oral kalsiyum replasmanı kesilerek taburcu edildi. İki olguda ise transplantasyon başarısız oldu ve onlara ikinci kez paratiroid ototransplantasyonu uygulandı. İkinci transplantasyon sonrası intravenöz kalsiyum kesilerek hastalar taburcu edildi. Hiçbir olguda 18 aylık gözlem süresinde herhangi bir yan etki veya komplikasyon görülmedi.

Sonuç: Dondurularak saklanmış paratiroid dokusunun ototransplantasyonu, şiddetli hipokalsemi için en etkili ve kalıcı tedavi seçeneğidir. Bu transplantasyonu yapmak zor değildir ancak bu işlem için kriyoprezervasyon laboratuvarı ve deneyimli laboratuvar ekibi gereklidir. SH cerrahisi yapılan merkezlerde bu laboratuvarın bulunması mortalite ve morbidite riskini azaltmaktadır.

Anahtar Kelimeler: Kriyoprezervasyon, paratiroid, şiddetli hipoparatiroidizm, ototransplantasyon



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Cite this article as/Atıf: İdiz UO, Yücesan E, Göncü B, Özdemir B, Aysan E, Gürol AO. The Importance of Cryopreserved Parathyroid Tissue Autotransplantation in the Hypoparathyroidism Treatment after Secondary Hyperparathyroidism Surgery. İstanbul Med J 2021; 22(4): 275-9.

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Received/Geliş Tarihi: 28.06.2021

Accepted/Kabul Tarihi: 21.08.2021

Introduction

Secondary hyperparathyroidism (SH) is usually associated with chronic renal failure (1-3). Parathyroidectomy is required in 15% of patients undergoing dialysis within the first 10 years and 38% during the first 20 years (4-6). Total parathyroidectomy or subtotal parathyroidectomy with intraoperative parathyroid autotransplantation is the most common surgical procedure (1-3). One of the major complications observed after any thyroidectomy and SH surgery is hypoparathyroidism. Transient hypoparathyroidism after SH surgery occurs in up to 90% of patients, whereas permanent hypoparathyroidism in up to 20% (3).

Parathyroid autotransplantation was first described by Halsted (7) in dogs. This procedure was later extensively used in thyroid surgeries (in cases of accidentally removed parathyroid tissues) and SH surgeries (8-10). The parathyroid autotransplantation was traditionally performed as an intraoperative procedure with fresh tissues. According to subsequent scientific and technological developments, excised fresh tissues transferred from operating rooms to the laboratories were frozen to preserve their viability. Thus, many tissues such as the ovum, sperm, pancreas islet cells, meniscus, trachea, teeth, and parathyroid are safely cryopreserved and de-froze for auto or allotransplantation when necessary (11).

Cryopreserved parathyroid autotransplantation (CPA) was first performed by Wells and Christiansen (12) in 1974. Later, this process was used with different techniques in many scientific studies (13,14).

SH operations are performed in many centers; however, the CPA was not a widespread procedure due to the high cost in setting up the cryopreservation laboratory and qualified personnel requirements.

Cryopreservation laboratory is necessary for SH surgery performing centers because severe hypocalcemia causes a cardiac arrhythmia, fibrillation, and cardiac arrest. Serious risks severe hypocalcemia cases need continuous intravenous calcium replacement and intensive hospital care (15).

In this study, we presented our results of CPA in cases of severe hypocalcemia after SH surgery.

Methods

A retrospective clinical research was designed and applied to the local human ethics committee. After research protocol approval by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2879, date: 18.06.2021), informed consent was obtained from all participants. A total of 150 patients (age range: 26-69 years, mean age: 39.5 years, men/women: 2/1) underwent SP between June 2013 and December 2017 in the department of endocrine surgery. All patients underwent standard subtotal parathyroidectomy, which removed all three parathyroid tissues and half of the fourth parathyroid tissue. Excised parathyroid tissues were cut into two pieces. One piece was sent to the pathology laboratory for histopathological examination and the other piece was prepared to be sent to the cryopreservation laboratory.

The parathyroid capsule and other surrounding tissues were carefully dissected from the parathyroid tissues to be sent to the cryopreservation

laboratory. After washing the tissues several times with physiological saline, they were transferred to the laboratory by placing them in Falcon tubes of 15 mL volume containing phosphate buffer solution (PBS). Cell isolation was performed according to the protocol described below.

Parathyroid Cell Isolation and Cryopreservation

Tissues were received in the laboratory by an experienced biologist. In a negative pressure sterile cabinet, tissues are taken into a sterile vial shredded mechanically with a scalpel and filtered with a cell strainer (70 µm, BD Biosciences®, USA). Filtered cells are collected in 5 mL PBS and centrifuged at 270 g for 5 min at room temperature. The supernatant was removed, and cells were re-suspended in 1 mL PBS. Cell viability was assessed with a Muse™ Cell Analyzer (Merck Millipore®, Germany). Cells were cryogenically stored in PBS containing 10% of dimethyl sulfoxide (AppliChem®, Germany) using an isopropanol-based freezing container and then stored in a liquid nitrogen tank.

The cells are prepared for transplantation according to the protocol described below when CPA is decided in patients whose cells were previously cryopreserved.

Preparation of Cells for Transplantation

The cells in the liquid nitrogen tank were removed and placed in an incubator (ESCO, Singapore) at 37 °C with a 5% carbon dioxide-humidified atmosphere. After cultivation for approximately 72 hours, cells were collected and centrifuged at 270 g for 7 min at room temperature. The supernatant was removed and cells were re-suspended in 2 mL PBS. Cells were counted with cell counters, and an average of 70×10^6 cells was injected into the deltoid muscle of the non-dominant arm of patients.

After the transplantation, patients were observed in the endocrine surgery clinic. Intravenous calcium supplementation was gradually reduced. The patient was discharged when he became asymptomatic without taking any intravenous calcium and his serum calcium and parathormone (PTH) levels were elevated. Discharged patients were followed up weekly during the first month; then at 2, 4, and 6 months; and finally, at 6-month intervals at the outpatient clinic.

Statistical Analysis

Data of patients were entered into the Statistical Package for the Social Sciences 21 (IBM, Armonk, NY, USA) program, and the desired parameters were given by specifying the mean \pm standard deviation, as well as the minimum and maximum values.

Results

Severe hypocalcemia was accepted as a serum calcium level of 6.5 mg/dL or less in the postoperative period. Symptomatic severe hypocalcemia at postoperative day one was observed in 23 (15.3%) of 150 patients. Mean serum calcium level was 5.61 ± 3.05 mg/dL (range: 4.0-6.5 mg/dL) and the mean serum PTH level was 62.63 ± 125.68 pg/mL (range: 0-285 pg/mL). These patients were followed for 1 week with intravenous and oral calcium plus vitamin D supplementation, which is a routine practice in our clinic. Up to the seventh postoperative day, 16 (10.7%) patients

did not require intravenous calcium supplements; their symptoms almost disappeared, and were discharged. Intravenous and oral calcium plus vitamin D supplementations were administered; however, the serum calcium levels remained below 6.5 mg/dL in 7 (4.6%) patients and continued to be symptomatic. All patients were evaluated in the endocrine council and CPA was decided.

The mean age of the seven patients who underwent CPA was 44.5 ± 8.5 (range: 22-56) years, and the female to male ratio was 1.33. The serum PTH and calcium changes of patients are shown in Table 1, 2.

After CPA, except for two cases, serum PTH and calcium levels increased, symptoms decreased, intravenous calcium supplementation ceased, and patients were discharged. However, serum PTH and calcium levels were decreased at very low levels in cases 1 and 2. In case 1 serum PTH levels were 3 pg/mL and 1.3 pg/mL, serum calcium level at 6 mg/dL and 5.5 mg/dL in postoperative week 1 and month 1, respectively. In case 2, serum PTH levels were 2.5 pg/mL and 2.5 pg/mL and serum calcium level were 5.5 mg/dL and 5.6 mg/dL in postoperative week 1 and month 1, respectively (Table 1, 2). Occasional intravenous calcium infusion is required and symptoms persisted. In these cases, the second CPA was performed 3 months after the first transplantation. Serum PTH and calcium levels increased, symptoms disappeared, and intravenous calcium supplementations were ceased.

Serum PTH and calcium values were observed in all cases, which underwent CPA, at least 18 months (range: 18-25 months). None of the patients required intravenous or oral calcium supplementation. Only cases 1 and 2 were continued to take oral calcium effervescent tablets daily. None of the patients had local or systemic side effects or complications.

Discussion

Severe hypoparathyroidism is a rare complication of thyroid and SH surgery (3,16). When hypoparathyroidism is not severe, patients are discharged from the hospital with oral calcium and vitamin D preparations. In severe hypocalcemia, patients are impossible to be discharged due to continuous intravenous calcium infusion.

Falls due to muscle spasms or weakness and fall-related bone fractures are the main morbidity mechanisms, and cardiac arrest due to hypocalcemic myocardial fibrillation is the main mechanism of mortality of these cases (15). Four options for severe hypoparathyroidism management are as follows: a continuous intravenous calcium infusion, subcutaneous recombinant PTH injection, parathyroid allotransplantation, and CPA (13,17-19).

Continuous intravenous calcium infusion is an easy and inexpensive option; however, this approach requires appropriate hospital conditions and follow-up by an experienced clinician. Rapid and high-dose infusions increase the risk of myocardial fibrillation. The clinical effect of intravenous calcium infusion occurs rapidly (within minutes), but with short-term effectiveness (within hours) (17,20).

A recombinant PTH injection is a fast-acting option like an intravenous calcium infusion and does not require follow-up in hospital settings (21). However, it is very expensive and, in many countries, is not covered by the social insurance system.

Parathyroid allotransplantation is a process that requires a specific laboratory, experienced multidisciplinary staff from the clinical (internal medicine, endocrinology, endocrine surgery, etc), and biological sciences (22,23). In the literature, some case reports and very limited clinical series are available about parathyroid allotransplantation (19,23).

Table 1. PTH (pg/mL) value changes of the autotransplantation cases

	Preop	Postop day 7	Post Tx week 1	Post Tx month 1	Post Tx month 3	Post Tx month 6	Post Tx month 12	Post Tx month 18
Case 1	2308	1.9	3	1.3	12.9*	14	14	14
Case 2	>3500	0	2.5	2.5	7.5*	11	12	12
Case 3	>3500	18	19	19	19	21	19	19
Case 4	3235	67	70	75	74	87	85	85
Case 5	2764	28	32	34	38	38	38	38
Case 6	>3500	22	21	19	26	22	17	20
Case 7	2700	15	19	21	20	21	19	21

*: Second Tx performed, PTH: Parathormone, Preop: Preoperative, Postop: Postoperative

Table 2. Calcium (mg/dL) value changes of the autotransplantation cases

	Preop	Postop day 1	Post Tx week 1	Post Tx month 1	Post Tx month 3	Post Tx month 6	Post Tx month 12	Post Tx month 18
Case 1	9.7	6.1	6	5.5	6.4*	6.9	6.8	6.8
Case 2	11.9	5.7	5.5	5.6	6.1*	6.9	6.8	7
Case 3	10.4	4	4.8	5.1	7.6	8	7.8	8
Case 4	9.7	6.1	7.7	8	8.3	8.1	8.7	8.5
Case 5	10	5.3	6.8	6.9	7	8.1	7.5	8.1
Case 6	9.3	4.9	6.1	7	8.1	7.8	7.2	7.8
Case 7	9.4	5.7	6.2	6.4	6.4	6.8	6.9	6.9

*: Second Tx performed, Preop: Preoperative, Postop: Postoperative

Our center is the unique parathyroid allotransplantation center in Turkey approved by the Turkey Ministry of Health. In our center, tissues obtained from SH surgery as donors in parathyroid allotransplantations are used. Therefore, many patients who underwent SH are referring to our center, thus many SH surgeries are performed (24).

CPA is one of the most effective and also natural treatment options if excised parathyroid tissues are cryopreserved during SH surgery (25). Since the patient's tissues are used, an immunological reaction is not a risk, thus no immunosuppression is required (14,26). The most important limitation of this treatment option is the need for a specific cryopreservation laboratory and experienced biologist staff.

Different results were reported in the literature regarding the success of autotransplantation after cryopreservation of parathyroid tissue (14,26,27). Shepet et al. (27) reported that four patients who developed severe hypoparathyroidism after SH surgery underwent a CPA, of which only 1 was successful. Agarwal et al. (14) reported a success rate of 100% as a result of CPA in nine patients.

Schneider et al. (26) reported a 100% success rate in a series of 606 patients who underwent SH surgery and 13 patients who received CPA due to severe hypoparathyroidism. Another study reported that CPA was performed in a total of 25 patients with severe hypoparathyroidism following surgical interventions (secondary, persistent, and recurrent hyperparathyroidism) with different indications. Complete success was reported in 16 patients and partial success in 9 (28).

The significant differences in CPA success rates in the literature are mainly due to the laboratory process, as well as the donor cell quality and quantity (14,26,27). The laboratory process has two main stages: freezing and de-freezing (14,29). Freezing is start when the tissues are removed from the patient. This stage consists of multiple steps, including fast transportation from the operating room to the laboratory at a body temperature, cell isolation into the sterile cabin, centrifugation, cell storage in proper medium, -80 °C freezing in one night, and transfer to the liquid nitrogen tank. The de-freezing stage consists of taking cells out of the liquid nitrogen tank and heating them to 36 °C, culture medium incubation, cell counting, transportation to the patient room in a sterile tube at body temperature, and transplant to the patient via intramuscular injection (14,30). Incorrect and inadequate implementation of any of these steps will affect all subsequent steps and will therefore determine the CPA's success.

In 150 cases, the incidence of hypoparathyroidism was 4.6% (7 cases) in our series, who underwent SH surgery, which is consistent with other series in the literature (3,6). Our CPAs were performed with three experienced laboratory staff (two postdocs and one medical biologist) in our parathyroid transplant laboratory with specific devices for parathyroid tissue. Our relatively high success rate is related to our experienced surgical team, laboratory team, and laboratory infrastructure.

In two cases, second transplantation was performed because symptoms persisted and serum calcium and PTH levels were not elevated. After the second transplantation, symptoms disappeared, and serum calcium and

PTH levels were elevated, thus intravenous calcium infusion was ceased and cases were discharged from the hospital.

Conclusion

Therefore, severe hypocalcemia is a rare but life-threatening complication of SH surgery. In addition to oral supplementation, these cases require continuous intravenous calcium infusion in hospital conditions. CPA is the most effective and lasting treatment option for these cases. CPA is not difficult to perform but it necessitates a cryopreservation laboratory and experienced laboratory team. The presence of this laboratory in SH surgery performing centers reduces the risk of mortality and morbidity.

Ethics Committee Approval: This study approval by the University of Health Sciences Turkey, Istanbul Training and Research Hospital Ethics Committee (approval number: 2879, date: 18.06.2021).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - U.O.İ., E.A.; Design - U.O.İ., E.A.; Supervision - E.A.; Resources - U.O.İ., E.Y., B.G., B.Ö.; Materials - U.O.İ., E.Y., B.G., B.Ö.; Data Collection or Processing - U.O.İ., E.Y., B.G., B.Ö., E.A.; Analysis or Interpretation - U.O.İ., E.Y., B.G., B.Ö., E.A.; Literature Search - U.O.İ., E.Y., B.G., B.Ö., A.O.G.; Writing - U.O.İ., E.Y., B.G., B.Ö.; Critical Review - E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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