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Parathyroid cryopreservation following parathyroidectomy: a worthwhile practice?

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Abstract

Background—Parathyroid cryopreservation is often utilized for patients having parathyroidectomy. This allows for future autotransplantation if a patient becomes permanently hypocalcemic after surgery. However, the practice of cryopreservation is costly and time consuming, while the success rate of delayed autotransplantation is highly variable. We sought to determine the rate and outcomes of parathyroid cryopreservation and delayed autotransplantation at our institution to further evaluate its utility.

Methods—At our institution, 2,083 parathyroidectomies for hyperparathyroidism (HPT) were performed from 2001–2010. Of these, parathyroid cryopreservation was utilized in 442 patients (21%). Patient demographics, preoperative diagnoses, and other characteristics were analyzed, as well as the rate and success of delayed autotransplantation.

Results—Of the 442 patients with cryopreservation, the mean age was 55 ± 1 years and 313 (70.8%) were female. 308 (70%) had primary HPT, 46 (10%) had secondary HPT, and 88 (20%) had tertiary HPT. Delayed autotransplantation of cryopreserved parathyroid tissue was used in 4 (1%) patients at an average time of 9 ± 4 months after initial surgery. 3 out of the 4 patients remained hypoparathyroid following this procedure. The one cured patient underwent the procedure only 4 days following the initial parathyroidectomy.

Conclusion—While cryopreservation was used in over 1/5 of patients undergoing parathyroidectomy, the need for parathyroid reimplantation was very low (1%). Furthermore, the success rate of parathyroid autotransplantation was poor in these patients. Therefore, the continued practice of parathyroid cryopreservation is questionable.

INTRODUCTION

Surgical intervention remains the only curative therapy for patients with hyperparathyroidism [1, 2]. In modern practice, parathyroidectomy has been associated with minimal morbidity and excellent cure rates when performed by experienced surgeons [2]. In patients undergoing parathyroidectomy for treatment of HPT, permanent hypoparathyroidism is a potential complication. We define permanent hypoparathyroidism as persistent hypocalcemia (< 3 months) secondary to a low PTH level, requiring calcium and vitamin D supplementation [3]. This complication can have serious consequences for the patient's quality of life and overall health status. These patients require expensive lifelong supplementation, frequent laboratory tests, and increased rates of hospital admissions [4]. In addition, higher rates of osteoporosis, cataracts, and cardiac or

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neurological dysfunction may be seen [5, 6]. Clearly, avoiding this complication is of great importance.

Currently the rate of permanent hypoparathyroidism following parathyroidectomy is estimated at 1% [4]. However, the risk depends on the extent of parathyroid tissue removal. For single adenomas removed via minimally invasive parathyroidectomy, the risk of permanent hypoparathyroidism is lower compared to subtotal or total parathyroidectomy [3]. Moreover, past studies have reported that approximately 10% of patients having initial parathyroidectomy for multiglandular hyperplasia and 30% of patients having reoperation for persistent or recurrent HPT will develop hypoparathyroidism following surgery [6].

To minimize the risk of permanent hypoparathyroidism following parathyroidectomy, several surgical methods have been devised. Immediate autotransplantation had been performed since 1926 but it has a risk of persistent hyperparathyroidism [7]. Delayed autotransplantation of parathyroid glands has been utilized since 1974 and it allows for avoidance of unnecessary immediate autotransplantation in patients who may be only transiently hypoparathyroid after surgery [8, 9].

While parathyroid cryopreservation is routinely utilized following subtotal or total parathyroidectomy, it appears that the rate of future utilization of the cryopreserved tissue (delayed autotransplantation) remains low [10, 11]. Furthermore, in cases where the cryopreserved tissue is reimplanted, the success rate of this procedure is highly variable [6]. For the present study we sought to determine the rates of parathyroid cryopreservation and reimplantation, as well as the outcomes of reimplantation at our institution, in order to further evaluate our current practices.

METHODS

A review of a prospective database was performed to identify all patients undergoing parathyroidectomy for hyperparathyroidism at our institution from 2001–2010. All cases in which parathyroid cryopreservation was utilized were subsequently identified in the database.

At our institution, cryopreservation is only utilized in parathyroid operations if three or more parathyroid glands are resected or if the status of the remaining parathyroid glands is unknown (most commonly in a re-operative case). We would only use cryopreservation in a case of minimally invasive parathyroidectomy if the patient had a previous contralateral parathyroidectomy or thyroidectomy and the status of the parathyroid gland was uncertain. Therefore, we only use cryopreservation in instances where two or more glands are resected or when all parathyroid glands are at risk for non-function.

Our protocol for cryopreservation was adopted from the original Wells protocol [8]. When parathyroid tissue is resected it is placed on ice and transported to a sterile hood for immediate processing. The tissue is first minced into 1–2 mm pieces and then treated with 3 mL of RPMI 1640 washing media containing penicillin and streptomycin and 20% fetal calf serum. After washing, 0.2 gm of tissue is added to a vial containing 0.5 mL of RPMI 1640 freezing media containing penicillin and streptomycin and 20% dimethyl sulfoxide.

The procedure is repeated several times to produce several vials of tissue. The vials are then placed in isopropanol and stored at -80°C overnight. The following day the vials are transferred to liquid nitrogen. When needed for delayed autotransplantation, the tissue is thawed in a 37°C water bath on the day of surgery. The tissue is then reimplanted in the brachioradialis muscle of the non-dominant forearm in several small pockets.

Patient demographics, preoperative diagnoses, and the rates of delayed autotransplantation of cryopreserved parathyroid tissue were determined. For cases where cryopreserved tissue was autotransplanted, post-operative PTH level was noted. This allowed for determination of the success of the reimplantation as a cure for permanent hypoparathyroidism based on a normal PTH range of 10–55 pg/mL.

RESULTS

2,083 parathyroidectomies for hyperparathyroidism were performed at the University of Wisconsin-Madison from 2001–2010. Parathyroid cryopreservation was utilized in 21% (n=442) of these patients. Of these 442 patients, the mean age was 55 ± 1 and 313 (70.8%) were female (Table 1). The most common preoperative diagnosis was primary HPT, followed by tertiary and secondary HPT (Table 1). In 80% (n=352) of patients, having less than one full parathyroid gland remaining following surgery was the primary indication for surgery. In the remaining 20% (n=90), concern for the viability of the parathyroid glands remaining was the primary indication (Table 2). This indication was primarily seen in patients undergoing previous or concurrent thyroidectomy or patients undergoing reoperation for persistent HPT. Of these 90 patients, 34 (8%) patients had a history of previous parathyroidectomy, 35 (8%) had previous or concurrent thyroidectomy and 21 (5%) patients had no prior surgery.

Of the 442 cases of parathyroid cryopreservation, delayed autotransplantation of the cryopreserved tissue was used in 4 patients (1%). Two of these patients were males, two were females, and the median age was 33.5 years old (Table 3). The average time from initial parathyroidectomy to reimplantation was 9 ± 4 months.

Following delayed autotransplantation (2-year follow-up), 3 out of the 4 patients remained hypoparathyroid, while 1 patient had a normal PTH level (Table 3). The patient with a successful autotransplant underwent this procedure only 4 days after initial parathyroidectomy. The remaining 3 patients had delayed autotransplantation at 11.4 ± 7.1 months following parathyroidectomy. Thus, of 442 total cases of cryopreservation, only 1 (0.2%) resulted in a successful delayed autotransplant.

Patient 1 (of the four undergoing delayed autotransplant) underwent initial parathyroidectomy for tertiary hyperparathyroidism following renal transplantation. At the time of parathyroidectomy, the patient also underwent concurrent immediate parathyroid autotransplantation. This initial graft showed mild PTH output for several months and decreased the patient's symptoms and calcium supplementation requirements. However, slightly over a year later the immediate autotransplant graft failed and the patient required delayed autotransplant. After delayed autotransplant, the patient had a wide range of PTH level fluctuations including readings in the low, normal, and high levels. This resulted in transient improvement in symptoms of hypocalcemia and decreased supplementation requirement. Approximately 2 years after delayed autotransplantation the patient's PTH level stabilized in the low range and the patient's symptoms of hypocalcemia recurred. Shortly after the patient was lost to follow-up so no further intervention could be performed.

Patient 2 underwent parathyroidectomy for primary hyperparathyroidism. Initially the parathyroid tissue left intact was functional after parathyroidectomy with improvement in symptoms of hypocalcemia and supplementation requirement. However, approximately one year later the tissue was not able to sustain a normal PTH level so delayed autotransplant was attempted. This attempt was unsuccessful as the PTH remained low and the patient had ongoing symptoms of hypocalcemia and required calcium supplementation.

Patient 3 underwent parathyroidectomy for primary hyperparathyroidism. Delayed autotransplantation was performed due to low PTH and symptomatic hypocalcemia. Following the autotransplant this patient had a transient improvement in symptoms. However, the patient ultimately continued to have a low PTH level and required the same amount of supplementation as they did before autotransplantation. Three years after the first autotransplant, a second autotransplant was performed. This attempt resulted in no improvement in PTH level and the patient continued to require calcium supplementation.

Patient 4 also underwent parathyroidectomy for primary hyperparathyroidism. This patient developed immediate symptoms of hypocalcemia and had a low PTH after parathyroidectomy. Therefore, this patient underwent a delayed autotransplant only 4 days after parathyroidectomy. This procedure was successful in restoring the patients PTH level into the normal range. Also, the patient had notable improvement in symptoms and a required no additional calcium supplementation.

DISCUSSION

The first technique of parathyroid gland cryopreservation was immediate autotransplantation into the sternocleidomastoid or brachioradialis muscle. This procedure was first performed in 1926 by Lahey, but was not widely utilized until the late 1960's [7]. This procedure may allow for maintenance of parathyroid hormone (PTH) levels following parathyroidectomy via the autotransplanted gland. However, immediate autotransplantation is problematic because not every patient undergoing parathyroidectomy will develop hypoparathyroidism. This means some patients will undergo unnecessary autotransplantation [3]. Also, autotransplantation may lead to persistent hyperparathyroidism or the autotransplanted gland may become hyperfunctional after a time period following surgery [4].

Parathyroid cryopreservation with the potential for delayed autotransplantation was first utilized in 1974 by Wells et al as an alternative to immediate autotransplantation [8]. This technique involves preparation and storage of the patient's parathyroid tissue at -80°C following parathyroidectomy [12]. The surgeon then has the option to reimplant the tissue at a later time should the patient become permanently hypoparathyroid following surgery [9]. Because only permanently hypoparathyroid patients receive the delayed implantation, the risk of hyperparathyroidism following parathyroidectomy is decreased compared to immediate autotransplantation [4]. A main limitation of this technique is loss of graft tissue viability over time during storage. Also, the graft may be deemed viable at the time of autotransplant, but may be non-functional once implanted [13]. Lastly, as in immediate autotransplantation, the implanted graft may become hyperfunctional resulting in hyperparathyroidism [4, 13].

Since the development of parathyroid cryopreservation in the 1970's, this technique has been widely utilized in modern practice following parathyroidectomy. The goal of cryopreservation is to provide a curative treatment option for patients experiencing permanent hypocalcemia following parathyroidectomy. However, the indications and protocols for cryopreservation are highly variable among different institutions. This has resulted in highly variable rates and outcomes of delayed autotransplantation, leaving the surgeon to question whether cryopreservation is a worthwhile procedure [13].

At our institution, cryopreservation was used in over 20% of all cases of parathyroidectomy over a 10-year period. However, of these 442 cases of cryopreservation, only 4 (1%) patients required delayed autotransplantation. Furthermore, delayed autotransplantation only provided a cure for 1 of these 4 patients (based on PTH levels). These findings indicate that while we use cryopreservation often, it appears to provide very little benefit for our patients.

Our findings are consistent with previous studies, which report a high rate of cryopreservation with variable success rates of delayed autotransplantation. In 1997, Caccitolo *et al* reported a lower cryopreservation rate of 4% and a delayed autotransplantation rate of 12%. The success rate of autotransplantation was 23% [10]. Also in a more recent (2010) multi-center study in France, Borot *et al* found that delayed autotransplantation of cryopreserved tissue was only autotransplanted in 2% of patients, with a low cure rate of 10% [10]. This study also pooled the results of 8 previous studies (Brennan *et al* [12], Wells *et al* [14], Saxe *et al* [15], Wagner *et al* [5], Herrera *et al* [16], Feldman *et al* [17], and Cohen *et al* [6]) and showed that the reported success rate of delayed autotransplantation has ranged from 17–83% [10].

From our data and previous studies it is clear that the rates of cryopreservation following parathyroidectomy are very high, yet the actual usage of cryopreserved tissue and the success of delayed autotransplant is low. This is problematic for multiple reasons. While cryopreservation is a relatively inexpensive procedure, the cost becomes significant when the total volume of cryopreservation is high. At some institutions the procedure is carried out by the hospital's clinical laboratory, which may involve fees for sample preparation for cryopreservation as well as annual storage fees. This is complicated by a lack of consensus on how long to keep cryopreserved tissue before discarding it. Furthermore, if the research laboratory carries out the procedure it requires the immediate attention of research lab staff, which is time consuming and often disrupts the workday [11].

In order to improve the utility of cryopreservation, stricter guidelines for the indications for cryopreservation may be needed. This would likely involve determining preoperative factors that place patients at a higher risk for developing permanent hypocalcemia after parathyroidectomy. Doing so would allow us to be more selective in our usage of cryopreservation. Also, currently there exists no universal protocol for cryopreservation or delayed autotransplantation. A careful reexamination of how the resected tissue is transported, prepared, stored, thawed, and reimplanted may result in improved success rates of delayed autotransplant. Lastly, an important future direction may be to determine how to more rapidly identify hypocalcemic patients after parathyroidectomy so that the delayed autotransplantation can occur at a shorter interval. This is important because past studies have demonstrated a time dependent loss of tissue viability during cryopreservation [18]. To do this, more intensive postoperative PTH monitoring would be indicated. However, this method would also increase costs and would have to be carefully weighed against the benefits.

In summary, a careful reflection on the current practice of parathyroid cryopreservation is necessary to improve the future application of this procedure. Doing so may allow us to decrease health care costs and provide an improved treatment option for patients with permanent hypocalcemia after parathyroidectomy.

CONCLUSION

While cryopreservation was used in over 20% of patients undergoing parathyroidectomy, the need for parathyroid delayed autotransplantation was very low (1%). Furthermore, the success rate of parathyroid autotransplantation was poor in these patients. Therefore, the continued practice of parathyroid cryopreservation is questionable.

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SYNOPSIS

This article reviews the current outcomes of parathyroid gland cryopreservation. The focus is on delayed parathyroid autotransplantation for surgical management of patients with permanent hypoparathyroidism following parathyroidectomy.

Table 1

Parathyroid cryopreservation patient demographics

N	442
Age (yrs)	55 ± 1
% Female	70.8%
Preoperative Diagnosis	
1° HPT	308 (70%)
2° HPT	46 (10%)
3° HPT	88 (20%)

Table 2

Indications for parathyroid cryopreservation

Surgical Indication	Diagnosis		
	1° HPT	2° HPT	3° HPT
Subtotal Parathyroidectomy	224 (73%)	44 (94%)	84 (93%)
Remaining gland(s) viability concern	81 (26%)	3 (6%)	6 (6%)
Total	305	47	90

Table 3

Parathyroid autotransplantation patient demographics

Patient	1	2	3	4
Age/Gender	45/F	38/M	29/M	80/F
Diagnosis	3° HPT	1° HPT	1° HPT	1° HPT
Time from cryo to delayed autotransplant (days)	429	498	99	4
Pre-delayed autotransplant PTH (pg/mL)	12	11	2	<1
2 yrs s/p delayed autotransplant PTH (pg/mL)	7	5	6	14
Surgical cure? (normal PTH range of 10–55 pg/mL)	No	No	No	Yes