Case Report

Replantation with cryopreserved parathyroid for permanent hypoparathyroidism: a case report and review of literatures

Hai-Guang Liu1,2, Zai-Chong Chen3, Xiao-Hua Zhang1, Kai Yang1

1Department of Surgical Oncology, The First Affiliated Hospital of Wenzhou Medical University, Fuxue Road No. 2, Wenzhou 325000, China; 2Department of Pathology, Southern Hospital of Southern Medical University, Guangzhou Road No. 1838, Guangzhou 510515, China; 3Reproductive Medicine Center, The First Affiliated Hospital of Wenzhou Medical University, Fuxue Road No. 2, Wenzhou 325000, China

Received December 17, 2014; Accepted February 11, 2015; Epub March 15, 2015; Published March 30, 2015

Abstract: Permanent postsurgical hypoparathyroidism is defined as insufficient parathyroid hormone (PTH) to maintain normocalcemia 6 months after surgery. It occurs mostly in reoperation for persistent or recurrent hyperparathyroidism. The treatment of long-term calcium and vitamin D supplement is burdensome and may cause iatrogenic complications. PTH replacement is potential but still under trials. Only replantation with cryopreserved parathyroid is an available treatment for patients to reduce or stop long-term drug administration. However, this treatment is not applied widely in developing countries, due to lack of experiences and skills. Herein, we reported a 58-year-old male presented a continuous elevated parathyroid hormone up to about 2342 ng/L and bone pain during hemodialysis for 6 years due to chronic renal failure. He underwent the first operation total parathyroidectomy and autotransplantation. After this operation, he suffered from a persistent calcemia and permanent hypoparathyroidism. After three times of replantation with cryopreserved parathyroid and dialysis with a high calcium dialysate, the low concentration of calcium was elevated and symptoms of hypocalcemia disappeared. However, PTH was not elevated significantly in the long term. It might be related to our nonstandard cryopreservation protocol and no microbiological and histological examinations before replantation, compared with other successful reports. Therefore, we suggest a standard cryopreservation protocol should be followed by non-experienced institutions, especially in developing countries. Furthermore, a high calcium dialysate is efficient to increase calcium concentration and alleviate symptoms of hypocalcemia. It may be an available treatment of persistent hypocalcemia and permanent hypoparathyroidism in dialysis patients.

Keywords: Hypocalcemia, cryopreservation, transplantation, parathyroidectomy, hyperparathyroidism

Introduction

Hypoparathyroidism is the most frequent complication of total parathyroidectomy for renal hyperparathyroidism. Due to long-term bone hungry syndrome, most of them are transient. It can be resolved by medical therapy with oral vitamin D and calcium supplement, intravenous calcium supplement and a high calcium dialysate [1] (Figure 1). If it does not recover in 6 months after operation, it is defined as permanent hypoparathyroidism [2]. The current medical treatments of permanent hypoparathyroidism contain calcium and vitamin D supplement. Long-term calcium and vitamin D supplement is a great burden to patients. Parathyroid hormone (PTH) replacement with PTH (1-34) or PTH (1-84) is a potential treatment. A few clinical trials showed that PTH replacement could reduce daily calcium and vitamin D supplement, increase bone mineral density and bone turnover [3-6]. However, it needs to resolve some problems such as long-term effects and side effects by large-scale trials before its clinical application. Its subcutaneous usage also causes inconvenience. Therefore, PTH replacement is not yet available for current treatment of permanent hypoparathyroidism. Replantation with cryopreserved parathyroid is an available choice for permanent hypoparathyroidism. Al-
Replantation of cryopreserved parathyroid

Figure 1. Current treatments of hypoparathyroidism. The treatments of transient hypoparathyroidism contain calcium and vitamin D supplement. High calcium dialysis is only for patients with renal failure. Besides, parathyroid hormone replacement is potential but still needs trials for permanent hypoparathyroidism. Replantation with cryopreserved parathyroid is an available treatment of permanent hypoparathyroidism.

Table 1. Success rates of cryopreserved parathyroid graft

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Number</th>
<th>Success rate</th>
<th>Longest duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brennan et al [8]</td>
<td>1979</td>
<td>USA</td>
<td>6</td>
<td>67%</td>
<td>18</td>
</tr>
<tr>
<td>Wells et al [9]</td>
<td>1980</td>
<td>USA</td>
<td>6</td>
<td>83%</td>
<td>≤ 6</td>
</tr>
<tr>
<td>Saxe et al [10]</td>
<td>1982</td>
<td>USA</td>
<td>12</td>
<td>58%</td>
<td>≤ 18</td>
</tr>
<tr>
<td>Herrera et al [12]</td>
<td>1992</td>
<td>USA</td>
<td>12</td>
<td>42%</td>
<td>11</td>
</tr>
<tr>
<td>Caccitolo et al [13]</td>
<td>1997</td>
<td>USA</td>
<td>13</td>
<td>46%</td>
<td>≤ 26</td>
</tr>
<tr>
<td>Feldman et al [14]</td>
<td>1999</td>
<td>USA</td>
<td>26</td>
<td>58%</td>
<td>125</td>
</tr>
<tr>
<td>Cohen et al [15]</td>
<td>2005</td>
<td>USA</td>
<td>26</td>
<td>69%</td>
<td>22</td>
</tr>
<tr>
<td>de Menezes Montenegro et al [16]</td>
<td>2007</td>
<td>Brazil</td>
<td>2</td>
<td>.9</td>
<td>30</td>
</tr>
<tr>
<td>Borot et al [17]</td>
<td>2010</td>
<td>France</td>
<td>20</td>
<td>20%</td>
<td>9</td>
</tr>
<tr>
<td>Schneider et al [18]</td>
<td>2012</td>
<td>Germany</td>
<td>15</td>
<td>100%</td>
<td>86</td>
</tr>
<tr>
<td>Shepet et al [19]</td>
<td>2013</td>
<td>USA</td>
<td>4</td>
<td>25%</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Leite et al [20]</td>
<td>2014</td>
<td>Brazil</td>
<td>1</td>
<td>.9</td>
<td>36</td>
</tr>
</tbody>
</table>

*: The success rate contain high, fully and partial functional cases. *: The longest duration of cryopreservation among high, fully functional or partial functional cases. #: Both the studies are case reports.

though first described by Wells et al [7] 40 years ago and followed by many clinics mostly in developed countries (Table 1), it is beginning to be conducted in our hospital in last three
Replantation of cryopreserved parathyroid
Replantation of cryopreserved parathyroid

years. Herein, we reported a case with permanent hypoparathyroidism and hypocalcemia after total parathyroidectomy and autotransplantation for renal hyperparathyroidism. The low concentration of calcium was elevated and symptoms of hypocalcemia disappeared after three times of replantation with cryopreserved parathyroid and dialysis with a high calcium dialysate. However, PTH was not elevated significantly. The causes of failure of our case and factors related to success of cryopreserved parathyroid graft were also discussed.

Case report

A 58-year-old male presented a continuous elevated PTH up to about 1000 ng/L without paresthesias and bone pain during hemodialysis for 6 years due to chronic renal failure. He received a regular hemodialysis three times a week. Meanwhile, he suffered from diabetes more than 8 years and received insulin therapy. He was enrolled in our hospital because he began to have bone and joint pain half a year later with quite a few elevated biochemical markers, PTH 2342 pg/L (normal level 10-69 ng/L), calcium concentration 2.58 mmol/L (normal level 2.10-2.60 mmol/L), phosphorus concentration 2.13 mmol/L (normal level 0.90-1.50 mmol/L), alkaline phosphatase 846 U/L (normal level 53-128 U/L). Ultrasound examination revealed that a hypoechoic and inhomogeneous nodule about 20 × 12 × 12 mm³ located close to the upper pole of the left lobe, another two similar nodules were close to the inferior pole of the right lobe and three hypoechoic and cystic nodules in the thyroid glands (Figure 2A and 2B).

The first operation: total parathyroidectomy and autotransplantation

He underwent an operation of lobectomy of the right thyroid gland, total parathyroidectomy and transplantation half a parathyroid gland into muscles of the right forearm in July 9, 2012. Meanwhile, the residual parathyroid was cryopreserved. The pathological examination showed thyroid nodular goiters and parathyroid hyperplasia (Figure 2C and 2D). Calcium concentration and PTH deceased immediately after operation. The lowest concentration of calcium was 1.07 mmol/L and PTH was 3 ng/L after several days. Therefore, an aggressive therapy with oral and intravenous calcium supplement was given. He was discharged when calcium concentration increased to 2.1 mmol/L eight days after operation, but PTH was still below normal. He went on to receive oral and intravenous calcium supplement after discharge. Meanwhile, he received a
The second operation: replantation with cryopreserved parathyroid

The symptom was similar without alleviation 6 months after operation. He underwent the second operation: replantation with cryopreserved parathyroid into the same forearm in January 17, 2013. Three pieces of about 3 × 3 × 3 mm³ cryopreserved parathyroid tissues were thawed, cut into 1 × 1 × 1 mm³ pieces and injected into muscles of the forearm. PTH from grafted forearm increased to 420 ng/L one week later and decreased to 37 ng/L 1.5 months later (Figures 3 and 4). Meanwhile, he went on to receive oral calcium supplement without vitamin D. Paresthesias still appeared every Monday 3 months after the second transplantation.

The third operation: replantation with cryopreserved parathyroid

He underwent the third operation: replantation with cryopreserved parathyroid into the same forearm in April 17, 2013. PTH from grafted forearm increased to 118 ng/L 3 days later. Calcium concentration increased to 2.06 mmol/L, but decreased to 1.63 mmol/L 9 days later (Figures 3 and 4). The symptom got a little alleviation 9 days later, but aggravated again half a month later. 1.5 months after operation, he began to receive hemodialysis with 2.0 mmol/L calcium dialysate, then calcium concentration increased close to the normal level, and paresthesias disappeared. Then he decreased oral calcium supplement.

The fourth operation: replantation with cryopreserved parathyroid

The calcium concentration was close to normal by oral calcium supplement and hemodialysis with 2.0 mmol/L calcium dialysate. The PTH was still in the low limit of normal. Due to the chance of renal transplantation, he wanted to...
receive the fourth operation to improve the calcium and PTH level without calcium supplement and dialysis after renal transplantation. He underwent replantation with cryopreserved parathyroid into muscles of the right forearm by open surgery in April 4, 2014. PTH from grafted forearm increased to 242 mmol/L, but from non-grafted forearm increased only a little. 20 days later, PTH still increased a little and calcium concentration was similar with preperation (Figures 3 and 4).

For better understanding, a diagrammatic sketch was made according to the process and outcome of the treatments (Figure 5).

Discussion

Herein, a patient with permanent hypoparathyroidism underwent four operations in our hospital. He was replanted with cryopreserved parathyroid in the last three operations. The duration of storage was 6 months, 9 months and 21 months between the first operation and the second, the third, the fourth operation respectively. The levels of PTH were higher from grafted forearm than from non-grafted forearm in the short term, but usually decreased 1 month later. The outcomes demonstrated that the cryopreserved parathyroid was active in the short term but reduced function in the long term. The success rate of the third operation satisfied us, but not the patient. Due to the chance of renal transplantation, he underwent the fourth operation to improve the calcium and PTH level to normal without calcium supplement and dialysis after renal transplantation. To date, there is no definite guideline about whether to transplant cryopreserved parathyroid for hypoparathyroidism but without hypocalcemia before renal transplantation. Based on the clinical effects of replantation, it could be considered as partial success in the short term. However, according to definitions for the function of cryopreserved parathyroid graft (Table 2) [2, 17], it should be defined as non-function for dialysis patients in the long term.

We searched for all papers related to replantation with cryopreserved parathyroid published in MEDLINE (National Library of Medicine, Bethesda, MD) from 1974 to 2014. The success rates of replantation with cryopreserved parathyroid vary from 20% to 100% [8-15, 17-19] (Table 1). Many factors affect the success of cryopreserved parathyroid graft. The function of cryopreserved parathyroid is the most important. Guerrero MA [21] found only 11 of 106 cryopreserved parathyroid specimens were viable. Only 1 of 92 specimens was viable when they were stored more than 24 months. On the contrary, 10 of 14 were viable when less than 24 months. A similar result was reported by Cohen MS [15]. Functional graft with cryopreserved parathyroid was only observed below 22 months of storage. Borot S

| Table 2. Definitions of parathyroid graft functional status according to different patients |
|-----------------------------------------------|-------------|---------------|----------------|
| Non-functional                               | Partially functional | Fully functional |
| Dialysis patients                            | PTH ≤ 20 | 20 < PTH ≤ 50 | 50 < PTH ≤ 300 |
| Non-dialysis patients                        | The same supplement | Decreased supplement | Without supplement |
|                                             | PTH ratio ≤ 1.5 | PTH ratio ≥ 1.5 | PTH ratio ≥ 1.5 |

The supplement contains calcium and vitamin D administration.
reported only 4 of 20 grafts were functional from a retrospective multicenter study in France [17]. All of 4 grafts were cryopreserved less than 1 year. Therefore, it may be reasonable to disposal parathyroid specimen stored more than 24 months. However, Schneider R reported a 100% success rate of cryopreserved parathyroid in 15 permanent hypothyroidisms. 4 of them were cryopreserved than 2 years and the longest one was 86 months [18]. Several previous studies also displayed that the duration of cryopreservation was not closely related to the viability of cryopreserved cells in vitro [22-24] and the function in vivo [25]. From Table 1, the longest duration among the successful replantation was 125 months. Therefore, the duration of cryopreservation (6 months, 9 months and 21 months) might not be the main cause of failure in our case.

Recently, there are two ways of parathyroid transplantation by open surgery or by subcutaneous injection. Transplantation by open surgery is widely used, because it favors surgeons easy to re-explore hyper-functional grafted parathyroid by marks during operation. However, it leads to a long operation time, a big injury for grafted sites and possible general anesthesia. To avoid these shortcomings, transplantation by subcutaneous injection with local anesthesia may be a better choice. Two studies reported that the successful parathyroid transplantation by subcutaneous injection was similar with by open surgery, but with less complication and more convenience [26, 27]. Only one graft was hyper-functional, but it was easy to remove it [26]. Herein, the patient underwent four operations of parathyroid transplantation. The first and fourth were by open surgery, and the second and third were by subcutaneous injection. During the first operation, parathyroid transplantation was easy to mark without extra anesthesia simultaneously following total parathyroidectomy in case of re-exploration of hyperparathyroidism, which was also the reason of the fourth operation by open surgery. To save time of transporting thawed parathyroid from cryopreservation lab to opera-
Replantation of cryopreserved parathyroid

tion room, parathyroid was implanted by subcutaneous injection during the second and third operation. What is the better way is still not definite. Currently, a proper way is favorable without loss of function, but with more convenience and less invasive injury. Therefore, the transplantation way might affect little on the failure of replantation with cryopreserved parathyroid in our case.

Some other factors also influence the success rate (Figure 6), such as the number of replanted fragments [28], microbiological and histological examination before replantation [18, 29]. Wagner PK suggested that 30-40 pieces of 1 mm³ were sufficient in case of cryopreserved parathyroid with partial necrosis [22]. In our case, three pieces of about 3 × 3 × 3 mm³ were thawed and replanted. The number was enough, but the activity was not examined before replantation. Schneider R only replanted tissues without necrosis or microbiological contamination by microbiological and histological examinations before replantation, and then they obtained a 100% success rate [18]. Stotler BA found 5 types of bacteria were present in 11 cryopreserved parathyroid tissues among 47 samples [29]. Thus, it is necessary to do microbiological examinations before replantation. We did not do microbiological and histological examinations before replantation due to lack of experiences of replantation. This might cause the failure in the long term in our case. Another reason might be the size of cryopreservation. Tissues were cryopreserved in the lab of reproductive medicine centre of our hospital without any cost. To reduce the costs, we cryopreserved three pieces of about 3 × 3 × 3 mm³ in a tube. This was different from the standard size of 1 × 1 × 1 mm³, which needs more places and more costs. Besides, a standardized freezing and thawing protocol [30], the transporting time between resection and freezing, thawing and transplantation [18] also affect the success of replantation with cryopreserved parathyroid.

Acknowledgements

The patient was informed and agreed to publish the pictures in any scientific journals.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kai Yang, Department of Surgical Oncology, The First Affiliated Hospital of Wenzhou Medical University, Fuxue Road No. 2, Wenzhou 325000, China. Tel: +86057755-789462; Fax: +865578999618767; E-mail: yangk-wzmc@yahoo.com

References

Replantation of cryopreserved parathyroid


