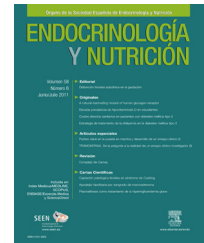




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EDITORIAL

Parathyroid transplantation[☆]

Autotrasplante de paratiroides

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Postoperative hypoparathyroidism is one of the most significant complications of thyroid and parathyroid surgery, and of cancer surgery in the anterior triangle of the neck. Clinical manifestations, which may range from mild to fatal due to asphyxia secondary to laryngospasm and/or bronchospasm depending on the severity of hypocalcemia, require lifetime replacement therapy, frequent laboratory test monitoring, or hospital admissions for IV administration of calcium, which severely impair the quality of life of these patients. In addition to conventional treatment with calcitriol and calcium, and until adequate replacement with recombinant exogenous PTH^{1,2} or parathyroid cells obtained from embryonic stem cells³ is available, parathyroid autotransplantation, performed either during the same surgical procedure or at a later time, has been used in an attempt to prevent or minimize these significant sequelae.^{4,5}

Early experimental studies were conducted by Halsted, and the first report in humans was published by Lahey in 1926. However, its clinical value was not recognized until the 1970s when Wells developed and disseminated the surgical procedure for primary hyperparathyroidism.⁶ The main indications for parathyroid autotransplantation are currently well defined: (1) for surgical treatment of primary hyperparathyroidism due to multiglandular disease

(primary hyperplasia either associated or not with MEN syndromes); (2) in secondary hyperparathyroidism; (3) in repeat surgical exploration for persistent or recurrent hyperparathyroidism; and (4) during total thyroidectomy for thyroid carcinoma or benign disease (normal functioning and hyperfunctional multinodular goiter) and in cancer surgery in the anterior neck compartment.

Postoperative hypoparathyroidism may be: (1) transient, when the functional recovery of the parathyroid glands occurs within 3–6 months; (2) protracted, when this time period extends up to one year; and (3) permanent, when no functional recovery has occurred one year after surgery.⁷ The incidence of transient hypoparathyroidism ranges from 10% to 50%. This is on the assumption that a sufficient amount of viable parathyroid tissue remains to allow for the adequate recovery of parathyroid function. Permanent hypoparathyroidism occurs in only 1–10% of patients, with the highest rates found in patients undergoing repeat surgery. This complication may be prevented if the surgeon identifies and preserves at least one or two parathyroid glands and transplants, according to classical criteria, glands of doubtful viability or inadvertently removed. Although attempts have been made to use intraoperative measurement of PTH to establish the indication for autotransplantation,⁸ the true value of this proposal is highly questionable. In our experience (data not published), this test gives equivocal results for the prediction of hypocalcemia in the first 48 h after surgery.

Autotransplantation may be performed immediately or at a later time. Immediate transplantation of a single gland, as may occur during thyroid surgery, is usually done on the ipsilateral sternocleidomastoid muscle. In cases of delayed

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transplantation or transplantation of more than one gland or hyperplastic tissue, the anterior aspect of the non-dominant forearm is preferred. This site allows for measuring PTH gradients to diagnose potential graft hypofunction using the Casanova test.⁹ Other sites used include the greater pectoral muscle, abdominal wall fat and, more recently, the presternal subcutaneous space.

Delayed autotransplantation is reserved for patients with multiglandular disease due to primary hyperparathyroidism, including MEN syndromes, in whom total parathyroidectomy has been performed to prevent repeat neck surgery or because the initial graft has failed. Its value is highly controversial, however, because it has been shown that the viability of cryopreserved tissue is very uncertain from 12 to 24 months of storage, and an 80% failure rate is seen from 12 months.^{10,11} This procedure should therefore be reserved for highly specialized centers.¹¹

The function of the grafted parathyroid tissue has been adequately analyzed. After a period of temporary ischemia, spontaneous angiogenesis occurs due to a rapid increase in the expression of vascular endothelial growth factor.¹² The graft starts to be viable and functional at 20 days, although the latency time until adequate function is achieved is usually two months.¹³ This period may be as long as eight months with cryopreserved autografts. Clinically, grafts are classified as fully functional, partly functional, or non-functional. A graft is fully functional when the patient remains normocalcemic and asymptomatic after the discontinuation of replacement therapy; this is the essential requirement for establishing graft function. When transplantation is performed in the arm, there should be a greater than 1.5- or 2-fold gradient between PTH levels in the grafted and the non-grafted arm.¹⁰ The graft is partly functional when the patient needs treatment with calcium and/or calcitriol with a PTH gradient higher than 1.5. The graft is non-functional if the patient is hypocalcemic, requires replacement therapy, and the PTH gradient is less than 1.5. In patients with renal hyperparathyroidism, circulating PTH levels only are assessed, and grafts are considered to be fully functional if systemic PTH levels range from 50 to 300 pg/mL.¹¹ Although grafted normal glands may take up sestamibi¹⁴ and may occasionally become hyperfunctioning,¹⁵ functional recovery may not be complete under normal conditions. In 1980, Salander and Tiseel reported, using a calcium deprivation test, a latent hypoparathyroid state in 22% of patients which, according to current understanding, could be explained by the fact that the mean PTH value only reaches 43% of the preoperative value when early postoperative PTH is actually undetectable.¹⁶

The efficacy of parathyroid autotransplantation may have been overestimated. The efficacy of early autotransplantation in primary hyperparathyroidism has been estimated at 85–99%.⁶ However, the results are less positive if the above discussed clinical function criteria are used. Feldman et al.¹⁷ reported that the success rate of early autotransplantation ranged from 20% to 60%, with 41% non-functional, 20% partly functional, and 33% functional grafts. The success rate of cryopreserved grafts was 31%.

In thyroid surgery, the classical study by Olson et al.¹⁸ suggested a 54% incidence of initial hypocalcemia, which increased with the number of glands explored and decreased

to a final 1% rate of hypoparathyroidism due to a 99% success rate of autotransplantation. However, this low incidence of permanent hypoparathyroidism may not be due to autotransplantation alone, as these authors recognize that the effect exerted by the parathyroid tissue left *in situ* may not be known. This crucial fact, which would appear to call into question the final value of the autotransplantation of isolated glands for the prevention of permanent hypoparathyroidism in thyroid surgery, is based on four clinically documented observations. First, autotransplantation based on the color of the glands, i.e. theoretically devascularized, is equivocal because, although they are apparently ischemic, recovery occurs within a few weeks.¹⁹ Second, the incidence of permanent hypocalcemia is higher when more than two glands are transplanted (21.4%) than when only one (1.4%) or none (0%) is transplanted.¹⁶ Third, no significant differences are seen in the proportion of patients with permanent hypocalcemia between those with one gland transplanted (0%) and those with none transplanted (2.5%).²⁰ And fourth, recovery from prolonged hypocalcemia occurs in 78% of cases, with no documented protection of autotransplantation against permanent hypoparathyroidism.²¹

To sum up, despite doubts about the function of grafted glands and the variability of the results,⁵ the autotransplantation of parathyroid glands in thyroid surgery, which continues to be routinely, and perhaps empirically, used to prevent permanent hypoparathyroidism should be reserved for fully devascularized glands due to inadvertent or mandatory removal, and should in no case replace the best prevention technique known: careful surgery that preserves gland vascularization *in situ*.²² In thyroid surgery, autotransplantation should only be reserved for centers highly experienced in multiglandular disease and cryopreservation.

References

1. Cusano NE, Rubin MR, Sline Jr J, Bilezikian JP. Mini-review: new therapeutic options in hypoparathyroidism. *Endocrine*. 2012;41:410–4.
2. Díaz-Soto G, Mora-Porta M, Nicolau J, Perea V, Halperin I, Puig-Domingo M. Efficacy and safety of long term treatment of unresponsive hypoparathyroidism using multipulse subcutaneous infusion of teriparatide. *Hormone and Metabolic Research*. 2012;44:708–10.
3. Woods Ignatoski KM, Bingham EL, Frome LK, Doherty GM. Differentiation of precursors into parathyroid-like cells for treatment of hypoparathyroidism. *Surgery*. 2010;148:1186–9.
4. Walker Harris V, Jan de Beur S. Postoperative hypoparathyroidism: medical and surgical therapeutic options. *Thyroid*. 2009;19:967–73.
5. Moffett JM, Suliburk J. Parathyroid autotransplantation. *Endocrine Practice*. 2011;17 Suppl. 1:83–9.
6. Wells Jr SA, Ross 3rd AJ, Dale JK, Gray RS. Transplantation of the parathyroid glands: current status. *Surgical Clinics of North America*. 1979;59:167–77.
7. Larrañaga Barrera E. Hipocalcemia postoperatoria. In: Sitges-Serra A, Sancho Insenser J, editors. *Guías Clínicas de la Asociación Española de Cirujanos, Cirugía Endocrina*, 13, 2ª ed. Madrid: Editorial Arán S.L.; 2009. p. 177–83.
8. Barczyński M, Cichoń S, Konturek A, Cichoń W. Applicability of intraoperative parathyroid hormone assay during total thyroidectomy as a guide for the surgeon to selective

- parathyroid tissue autotransplantation. *World Journal of Surgery*. 2008;32:822–8.
9. Casanova D, Sarfati E, de Francisco A, Amado JA, Arias M, Dubost C. Secondary hyperparathyroidism: diagnosis of site of recurrence. *World Journal of Surgery*. 1991;15:546–50.
 10. Guerrero MA. Cryopreservation of parathyroid glands. *International Journal of Endocrinology*. 2010;2010. Article ID: 829540.
 11. Borot S, Lapierre V, Carnaille B, Goudet P, Penfornis A. Results of cryopreserved parathyroid autografts: a retrospective multicenter study. *Surgery*. 2010;147:529–35.
 12. Carter WB, Uy K, Ward MD, Hoying JB. Parathyroid-induced angiogenesis is VEGF-dependent. *Surgery*. 2000;128:458–64.
 13. Lo CY. Parathyroid autotransplantation during thyroidectomy. *ANZ Journal of Surgery*. 2002;72:902–7.
 14. Sierra M, Herrera MF, Herrero B, Jiménez F, Sepúlveda J, Lozano RR, et al. Prospective biochemical and scintigraphic evaluation of autografted normal parathyroid glands in patients undergoing thyroid operations. *Surgery*. 1998;124:1005–10.
 15. D'Avanzo A, Parangi S, Morita E, Duh QY, Siperstein AE, Clark OH. Hyperparathyroidism after thyroid surgery and autotransplantation of histologically normal parathyroid glands. *Journal of the American College of Surgeons*. 2000;190:546–52.
 16. Kihara M, Miyauchi A, Kontani K, Yamauchi A, Yokomise H. Recovery of parathyroid function after total thyroidectomy: long-term follow-up study. *ANZ Journal of Surgery*. 2005;75:532–6.
 17. Feldman AL, Sharaf RN, Skarulis MC, Bartlett DL, Libutti SK, Weinstein LS, et al. Results of heterotopic parathyroid autotransplantation: a 13-year experience. *Surgery*. 1999;126:1042–8.
 18. Olson Jr JA, DeBenedetti MK, Baumann DS, Wells Jr SA. Parathyroid autotransplantation during thyroidectomy. Results of long-term follow-up. *Annals of Surgery*. 1996;223:472–80.
 19. Promberger R, Ott J, Kober F, Mikola B, Karik M, Freissmuth M, et al. Intra- and postoperative parathyroid hormone-kinetics do not advocate for autotransplantation of dicolored parathyroid glands during thyroidectomy. *Thyroid*. 2010;20:1371–5.
 20. Testini M, Rosato L, Avenia M, Basile F, Portincasa P, Piccini G, et al. The impact of single parathyroid gland autotransplantation during thyroid surgery on postoperative hypoparathyroidism: a multicenter study. *Transplantation Proceedings*. 2007;39:225–30.
 21. Sitges-Serra A, Ruiz S, Girvent M, Manjón H, Dueñas JP, Sancho JJ. Outcome of protracted hypoparathyroidism after total thyroidectomy. *British Journal of Surgery*. 2010;97:1687–95.
 22. Thomusch O, Machens A, Sekulla C, Ukkat J, Brauckhoff M, Dralle H. The impact of surgical technique on postoperative hypoparathyroidism in bilateral thyroid surgery: a multivariate analysis of 5846 consecutive patients. *Surgery*. 2003;133:180–5.