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临床研究·论著

甲状腺全切除术后iPTH变化与PHP恢复时间的关系及对永久性PHP的预测价值*

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摘要: 目的 探讨甲状腺全切除术后血清甲状旁腺激素(iPTH)变化与甲状旁腺功能减退(PHP)恢复时间的关系及对永久性PHP发生的预测价值。**方法** 回顾性分析2017年1月—2021年9月在承德医学院附属医院行甲状腺全切除术的516例甲状腺癌及甲状腺良性病变患者的临床资料。统计患者术后血清iPTH恢复至正常参考值下限的时间及各时间段患者的分布情况。对比不同恢复时间患者术前、术后24 h血清iPTH水平。随访6个月,统计患者永久性PHP发生情况,并依据是否发生PHP分为发生组和未发生组。对比发生组和未发生组患者的临床资料。多因素一般Logistic回归模型分析甲状腺全切除术后永久性PHP发生的危险因素。制作受试者工作特征(ROC)曲线,以曲线下面积(AUC)分析血清iPTH水平对甲状腺全切除术后永久性PHP发生的预测价值。

结果 不同恢复时间甲状腺全切除患者术前iPTH水平比较,差异无统计学意义($P > 0.05$)。与恢复时间<1周患者比较,1~4周、1~3个月、4~6个月和>6个月患者术后24 h血清iPTH水平更低($P < 0.05$);与1~4周比较,1~3个月、4~6个月和>6个月患者术后24 h血清iPTH水平低($P < 0.05$);与1~3个月比较,4~6个月和>6个月患者术后24 h血清iPTH水平低($P < 0.05$);与4~6个月比较,>6个月患者术后24 h血清iPTH水平低($P < 0.05$)。两组患者性别、年龄、BMI、手术时间、结节最大直径、术后病理良恶性结果、是否合并桥本甲状腺炎、是否合并甲状腺功能亢进、是否包膜侵犯、是否行VI区、颈侧区及喉返神经后方淋巴结清扫、是否甲状旁腺自体移植、术前血磷、术前血钙、术前血清iPTH、术后24 h血磷比较,差异无统计学意义($P > 0.05$)。发生组¹³¹I治疗占比高于未发生组,术后24 h血钙及血清iPTH水平则低于未发生组($P < 0.05$)。多因素一般Logistic分析结果显示:术后¹³¹I治疗 [$\hat{OR} = 3.108$ (95% CI: 1.415, 6.829)]、术后24 h血钙 [$\hat{OR} = 2.768$ (95% CI: 1.036, 4.072)]、术后24 h血清iPTH [$\hat{OR} = 3.380$ (95% CI: 1.843, 8.104)]水平是甲状腺全切除术后发生永久性PHP的危险因素($P < 0.05$)。ROC曲线分析结果显示,血清iPTH水平对甲状腺全切除术后永久性PHP发生预测的敏感性、特异性及AUC分别为81.48%(95% CI: 0.613, 0.930)、76.69%(95% CI: 0.726, 0.803)、0.817(95% CI: 0.781, 0.850)。

结论 甲状腺全切除术后24 h血清iPTH水平与PHP恢复时间有关,术后24 h血清iPTH水平对永久性PHP发生的预测价值较高。

关键词: 甲状旁腺功能减退; 甲状腺全切; 甲状旁腺激素; 永久性甲状旁腺功能减退

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Correlation between iPTH changes and time to hypoparathyroidism recovery after total thyroidectomy and predictive value of iPTH levels for permanent hypoparathyroidism*

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Abstract: Objective To investigate the correlation between the changes of intact parathyroid hormone (iPTH) and the time to hypoparathyroidism (PHP) recovery after total thyroidectomy and the predictive value of iPTH levels for the occurrence of permanent PHP. **Methods** The clinical data of 516 patients with thyroid cancer or benign thyroid lesions who underwent total thyroidectomy in our hospital from January 2017 to September 2021 were retrospectively analyzed. The recovery time of the postoperative serum level of iPTH to the lower limit of the normal range and the distribution of the recovery time were determined. The serum levels of iPTH before the surgery and 24 hours after the surgery were compared among patients with different recovery time. After 6 months of follow-up, the occurrence of permanent PHP in the patients was observed, and the patients were subdivided into the occurrence group and the non-occurrence group according to whether PHP occurred or not. The clinical data of the patients in the occurrence group and the non-occurrence group were compared. The multivariable Logistic regression analysis was performed to determine the risk factors for the occurrence of permanent PHP after total thyroidectomy. The receiver operating characteristic (ROC) curve was plotted, and the predictive value of the serum level of iPTH for the occurrence of permanent PHP after total thyroidectomy was analyzed via the area under the ROC curve (AUC). **Results** There was no significant difference in preoperative iPTH levels in patients undergoing total thyroidectomy with different recovery time ($P > 0.05$). Compared with patients with recovery time shorter than 1 week, those with recovery time between 1 week to 4 weeks, 1 month to 3 months, 4 to 6 months and that longer than 6 months had lower serum levels of iPTH 24 hours after the surgery ($P < 0.05$). Compared with patients with recovery time between 1 week to 4 weeks, those with recovery time between 1 month to 3 months, 4 to 6 months and that longer than 6 months had lower serum levels of iPTH 24 hours after the surgery ($P < 0.05$). Compared with patients with recovery time between 1 month to 3 months, those with recovery time between 4 to 6 months and that longer than 6 months had lower serum levels of iPTH 24 hours after the surgery ($P < 0.05$). Besides, patients with recovery time longer than 6 months showed even lower serum levels of iPTH 24 hours after the surgery relative to those in patients with recovery time between 4 to 6 months ($P < 0.05$). The sex composition, age, BMI, the operative duration, the maximal diameter of the nodules, the malignancy of thyroid lesions, the proportion of patients complicating with Hashimoto's thyroiditis, the proportion of patients complicating with hyperthyroidism, the proportion of tumor capsular invasion, the proportions of lymph node dissection in the VI area, the lateral neck, and behind the recurrent laryngeal nerve, the proportion of parathyroid autotransplantation, preoperative serum levels of phosphorus, calcium, and iPTH, and the level of serum phosphorus 24 hours after the surgery were not different between the two groups of patients ($P > 0.05$). The proportion of patients undergoing I^{131} treatment in the occurrence group was higher than that in the non-occurrence group, and the serum levels of calcium and iPTH 24 hours after the surgery in the occurrence group were lower than those in the non-occurrence group ($P < 0.05$). The multivariable Logistic regression analysis showed that postoperative I^{131} treatment [$\hat{OR} = 3.108$, (95% CI: 1.415, 6.829)], the level of serum calcium 24 hours after the surgery [$\hat{OR} = 2.768$, (95% CI: 1.036, 4.072)], and the level of serum iPTH 24 hours after the surgery [$\hat{OR} = 3.380$, (95% CI: 1.843, 8.104)] were risk factors for the occurrence of permanent PHP after total thyroidectomy ($P < 0.05$). The ROC curve analysis revealed that the sensitivity, specificity and AUC of the serum iPTH level for predicting the occurrence of permanent PHP after total thyroidectomy were 81.48% (95% CI: 0.613, 0.930), 76.69% (95% CI: 0.726, 0.803), and 0.817 (95% CI: 0.781, 0.850), respectively. **Conclusions** The serum iPTH level 24 hours after total thyroidectomy is related to the recovery time of PHP, and exhibits a high predictive value for the occurrence of permanent PHP.

Keywords: hypoparathyroidism; total thyroidectomy; parathyroid hormone; permanent hypoparathyroidism

甲状腺全切除术后甲旁腺功能减退(Pseudohypoparathyroidism, PHP)可严重影响患者的生活质量,轻者出现手足麻木等症状,重者可致呼吸困难、肌肉痉挛等^[1]。相关研究报告,甲状腺全切除术后发生PHP较为常见,依据甲旁腺功能恢复时间可分为暂时性PHP和永久性PHP^[2-3]。永久性PHP对患者的影响更为严重,故在甲状腺全切除术

后早期预测和诊断永久性PHP,对临床制订治疗措施和改善预后具有重要的指导价值。既往临床中多采用血钙浓度评估永久性PHP,但由于血钙浓度受饮食中钙含量、肠钙吸收等多种因素的影响,其作为预测指标对永久性PHP进行评估效能较低,有一定的滞后性^[4-5],亟须寻求更为理想的指标预测甲状腺全切除术后永久性PHP。

血清甲状旁腺激素(intact parathyroid hormone, iPTH)作为调节机体钙磷代谢的一种激素,具有半衰期短等特点,同时其还对术后血钙的异常有较高的敏感性。有研究报道,术后血清iPTH水平与术后PHP的发生有关^[6]。但目前甲状腺全切除术后血清iPTH变化与PHP恢复时间的关系及对永久性PHP预测价值目前尚不清楚。鉴于此,本研究回顾性分析承德医学院附属医院行甲状腺全切除术的甲状腺癌及甲状腺良性病变患者的临床资料,针对上述问题进行探讨,现将研究结果作如下报道。

1 资料与方法

1.1 临床资料

回顾性分析2017年1月—2021年9月在承德医学院附属医院行甲状腺全切除术的516例甲状腺癌及甲状腺良性病变患者的临床资料。其中男性99例,女性417例;年龄22~73岁,平均(45.91±12.18)岁;体质量指数(body mass index, BMI)19.34~27.81 kg/m²,平均(22.63±2.69)kg/m²。纳入标准:①符合《甲状腺结节和分化型甲状腺癌诊治指南》^[7]诊断标准;②经术后病理证实;③符合手术指征,并行甲状腺全切除术;④单侧病变;⑤年龄>18岁;⑥美国麻醉医师协会(American Society of Anesthesiologists, ASA)^[8]分级I~II级;⑦临床资料完整。排除标准:①既往有颈部手术史;②合并骨质疏松、痛风等内分泌疾病;③心、肝、肾等重要脏器功能不全;④有精神疾病或认知功能障碍;⑤有放射治疗史;⑥严重消化道吸收功能障碍;⑦术前曾服用维生素D或钙剂补充治疗;⑧术前存在低血钙症或甲状旁腺异常;⑨不配合术后随访。根据是否发生永久性PHP将患者分为发生组和未发生组,分别有27和489例。本研究经医院医学伦理委员会批准,患者及家属签署知情同意书。

1.2 方法

1.2.1 血清iPTH检测 采集患者术前(手术当天)、术后24 h静脉血液5 mL,以3 200 r/min离心12 min,离心半径8 cm,分离血清,置于-20℃冰箱保存。采用全自动电化学发光免疫分析仪(型号:COB-SE601,德国罗氏公司)测定血清iPTH水平,试剂盒均购于上海恒斐生物科技有限公司。

1.2.2 手术及术后治疗 患者均行甲状腺全切除

术,术中采用精细化被膜分离技术原位保留甲状旁腺,若意外切除或血运受损的甲状旁腺需采用匀浆注射法,自体移植于胸锁乳突肌内。术后当天将2 g葡萄糖酸钙注射液(国药准字:H20153296,山东辰欣药业股份有限公司,规格:10 mL:1 g)加入150 mL生理盐水中静脉滴注;术后患者若出现低钙血症或血钙水平<2 mmol/L时需给予静脉补钙3 d,可依据患者病情适当延长,并逐步过渡为口服补充骨化三醇胶丸、碳酸钙;若2周后无钙血症应逐渐减少上述药品剂量。

1.2.3 永久性PHP判断 ①血清iPTH<15 pg/mL;②血钙<2.15 mmol/L;③需使用维生素D或钙剂缓解低钙血症有关症状^[9]。术后6个月出现上述情况中的1种即可判断为发生永久性PHP。

1.2.4 临床资料收集 收集并归纳可能影响甲状腺全切除术后永久性PHP发生的相关资料,包括性别、年龄、BMI、手术时间、结节最大直径、术后病理结果、是否合并桥本甲状腺炎、是否合并甲状腺功能亢进、是否包膜侵犯、是否行淋巴结清扫(VI区、颈侧区及喉返神经后方)、是否行甲状旁腺自体移植、术后是否进行¹³¹I治疗、术前和术后24 h血磷、血钙及血清iPTH水平。出院后6个月随访。

1.3 统计学方法

数据分析采用SPSS 21.0统计软件。计量资料以均数±标准差($\bar{x} \pm s$)表示,比较用t检验或单因素方差分析,两两比较用LSD-t检验;计数资料以构成比或率(%)表示,比较用 χ^2 检验;影响因素的分析用多因素一般Logistic回归模型;绘制受试者工作特征(receiver operating characteristic, ROC)曲线。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 不同恢复时间患者术前、术后24 h血清iPTH水平比较

不同恢复时间甲状腺全切除患者术前iPTH水平比较,经方差分析,差异无统计学意义($P > 0.05$)。不同恢复时间甲状腺全切除患者术后24 h血清iPTH水平比较,经方差分析,差异有统计学意义($P < 0.05$),与恢复时间<1周患者比较,1~4周、1~3个月、4~6个月和>6个月患者术后24 h血清iPTH水平更低($P < 0.05$);与1~4周相比,1~3个月、4~

6个月和>6个月患者术后24 h血清iPTH水平低($P<0.05$)；与1~3个月比较，4~6个月和>6个月患者术后24 h血清iPTH水平低($P<0.05$)；与4~6个月比较，>6个月患者术后24 h血清iPTH水平低($P<0.05$)。见表1。

表1 不同恢复时间患者术前、术后24 h血清iPTH水平比较 (pg/mL, $\bar{x} \pm s$)

恢复时间	n	术前血清iPTH	术后24 h血清iPTH
<1周	148	51.04 ± 15.03	29.14 ± 7.25
1~4周	162	48.21 ± 12.76	24.74 ± 6.19
1~3个月	138	47.53 ± 13.27	18.61 ± 5.13
4~6个月	41	47.08 ± 12.18	15.29 ± 3.75
>6个月	27	45.62 ± 11.76	10.16 ± 2.13
F值		1.919	109.656
P值		0.106	0.000

2.2 两组患者临床资料比较

两组患者性别、年龄、BMI、手术时间、结节最大直径、术后病理良恶性结果、是否合并桥本甲状腺炎、是否合并甲状腺功能亢进、是否包膜侵犯、是否行VI区、颈侧区及喉返神经后方淋巴结清扫、是否甲状腺旁腺自体移植、术前血磷、术前血钙、术前血清iPTH、术后24 h血磷比较，差异无统计学意义($P>0.05$)。两组患者术后 ^{131}I 治疗、术后24 h血钙、术后血清iPTH比较，差异有统计学意义($P<0.05$)，发生组 ^{131}I 治疗占比高于未发生组，术后24 h血钙及血清iPTH水平则低于未发生组。见表2。

2.3 影响甲状腺全切除术后永久性PHP发生的多因素一般Logistic回归分析

以术后 ^{131}I 治疗(否=0,是=1)、术后24 h血钙及血清iPTH水平(取值为实测值)为自变量，甲状腺全切除术后是否发生永久性PHP为因变量(未发生=

表2 发生组和未发生组患者临床资料比较

组别	n	男/女/例	年龄/(岁, $\bar{x} \pm s$)	BMI/(kg/m ² , $\bar{x} \pm s$)	手术时间/(min, $\bar{x} \pm s$)	结节最大直径/例		
						≤5 cm	>5 cm	
发生组	27	8/19	48.69 ± 13.27	22.18 ± 4.13	118.32 ± 30.21	21	6	
未发生组	489	91/398	45.76 ± 11.83	22.65 ± 4.69	112.75 ± 27.36	403	86	
χ^2 / t 值		2.004	1.245	0.510	1.024	0.375		
P值		0.157	0.214	0.610	0.306	0.540		
组别	术后病理结果/例			桥本甲状腺炎/例		甲状腺功能亢进/例		
	良性	恶性	是	否	是	否	是	否
发生组	2	25	8	19	2	25	10	17
未发生组	24	465	112	377	54	435	254	235
χ^2 / t 值		0.334		0.649		0.350		2.275
P值		0.563		0.421		0.554		0.131
组别	VI区淋巴结清扫/例		颈侧区淋巴结清扫/例		喉返神经后方淋巴结清扫/例		甲状旁腺自体移植/例	
	是	否	是	否	是	否	是	否
发生组	24	3	9	18	9	18	1	26
未发生组	385	104	120	369	132	357	14	475
χ^2 / t 值		1.606		1.055		0.518		0.064
P值		0.205		0.304		0.472		0.800
组别	术前血磷/(mmol/L, $\bar{x} \pm s$)		术后24 h血磷/(mmol/mL, $\bar{x} \pm s$)		术前血钙/(mmol/L, $\bar{x} \pm s$)		术后24 h血钙/(mmol/mL, $\bar{x} \pm s$)	
	(mmol/L, $\bar{x} \pm s$)	(mmol/mL, $\bar{x} \pm s$)	(mmol/L, $\bar{x} \pm s$)	(mmol/mL, $\bar{x} \pm s$)	(pg/mL, $\bar{x} \pm s$)	(pg/mL, $\bar{x} \pm s$)	(pg/mL, $\bar{x} \pm s$)	(pg/mL, $\bar{x} \pm s$)
发生组	1.49 ± 0.28	1.28 ± 0.21	2.14 ± 0.85	1.58 ± 0.41	45.62 ± 11.76	10.16 ± 2.13		
未发生组	1.52 ± 0.31	1.35 ± 0.26	2.21 ± 0.92	2.06 ± 0.59	48.78 ± 12.03	23.55 ± 5.01		
χ^2 / t 值		0.492	1.374	0.386	4.170	1.330		13.808
P值		0.623	0.170	0.699	0.000	0.184		0.000

0,发生=1)进行多因素一般Logistic回归分析, $\alpha_{入}=0.05$, $\alpha_{出}=0.10$,结果显示:术后 ^{131}I 治疗[$\hat{\text{OR}}=3.108$ (95% CI: 1.415, 6.829)]、术后24 h血钙[$\hat{\text{OR}}=2.768$

(95% CI: 1.036, 4.072)]、术后24 h血清iPTH [$\hat{\text{OR}}=3.380$ (95% CI: 1.843, 8.104)]水平是甲状腺全切除术后发生永久性PHP的危险因素($P<0.05$)。见表3。

表3 影响甲状腺全切除术后永久性PHP发生的Logistic回归分析参数

自变量	b	S_b	Wald χ^2	P值	$\hat{\text{OR}}$	95% CI	
						下限	上限
术后 ^{131}I 治疗	1.134	0.412	7.576	0.003	3.108	1.415	6.829
术后24 h血钙	1.018	0.432	5.553	0.021	2.768	1.036	4.072
术后24 h血清iPTH	1.218	0.376	10.493	0.000	3.380	1.843	8.104

2.4 血清iPTH水平对甲状腺全切除术后永久性PHP发生的预测价值

ROC曲线分析结果显示,血清iPTH水平对甲状腺全切除术后永久性PHP预测的敏感性、特异性及AUC分别为81.48%(95% CI: 0.613, 0.930)、76.69%(95% CI: 0.726, 0.803)、0.817(95% CI: 0.781, 0.850)。见图1和表4。

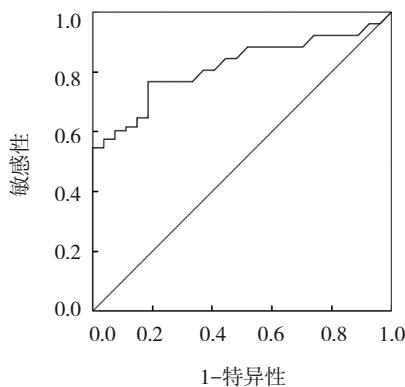


图1 血清iPTH水平预测甲状腺全切除术后永久性PHP的ROC曲线

3 讨论

PHP一直是困扰甲状腺外科治疗的难题,其中一部分为临时性,可有残余甲状旁腺代偿,但有部分为永久性PHP^[10-12]。有关研究报道,永久性PHP的发生率约为5%^[13-15]。目前临床中主要通过补充维生素D或钙剂对永久性PHP进行治疗,但患者仍会反复出现低钙血症,可对心血管、内分泌等系统造成损害,严重降低了患者的身体健康水平和生活质量。

本研究结果显示,甲状腺全切除术后24 h血清iPTH水平与PHP恢复时间存在一定的关系,甲状腺全切除术后PHP恢复时间越长,术后24 h血清iPTH

水平越低。分析其原因可能为,血清iPTH水平变化可一定程度上反映甲状旁腺的功能变化,其水平越低可能在甲状腺全切除术中对甲状旁腺的损伤越大^[16],越不利于PHP的恢复。甲状旁腺位于甲状腺后包膜,颜色与甲状腺组织类似,在甲状腺全切除术中有效识别、保护甲状旁腺是预防术后永久性PHP的关键,但在手术过程中受主刀医师操作技术、病灶部位等多因素的影响,不可完全避免损伤甲状旁腺,进而致使PHP、甚至是永久性PHP^[17-18]。本研究结果中甲状腺全切除术后永久性PHP发生率为5.23%,与既往侯大卫等^[19]研究结果的5.22%相近,进一步证实甲状腺全切除术后永久性PHP发生率较高。本研究结果表明,发生组 ^{131}I 治疗占比高于未发生组,术后24 h血钙及血清iPTH水平低于未发生组,并经多因素一般Logistic回归分析表明术后 ^{131}I 治疗、术后24 h血钙、术后24 h血清iPTH水平均是影响甲状腺全切除术后永久性PHP的危险因素。分析其原因可能为术后甲状腺恶性肿瘤进行 ^{131}I 放射治疗引发PHP可能是由于放射性 ^{131}I 衰变引发例子对邻近的甲状旁腺产生一定的电离辐射损伤,即旁观者效应^[20]。钙离子是维持机体活动所必需的离子,可维持细胞膜的生物电位、神经传导功能,进而影响肌肉的舒张、伸缩功能;永久性PHP患者多伴有低血钙,术后24 h血钙水平较低,可导致患者发生低钙血症,增加永久性PHP的发生风险。iPTH可直接调节机体钙磷代谢,术后24 h血清iPTH水平越低,甲状旁腺损伤越严重,并在短时间内难以恢复至正常水平^[21],故永久性PHP的发生风险越高。ROC曲线分析结果显示,血清iPTH水平对甲状腺全切除术后永久性PHP预测的敏感性、特异性及AUC分别为81.48%、76.69%、0.817,提示术后24 h血清

iPTH水平对永久性PHP的预测价值较高。分析血清iPTH水平可对永久性PHP进行预测的可能机制为：iPTH作为甲状旁腺主细胞所分泌的碱性单链多肽类激素，与甲状旁腺分泌功能密切相关，参与机体钙磷代谢的调节，其可通过增加血浆中钙离子的浓度，并作用于骨骼、肾脏，可影响肠道对钙离子的吸收；甲状腺切除术后血清iPTH水平降低可致使低钙血症，影响永久性PHP的发生。故而术后24 h血清iPTH水平对永久性PHP的预测价值较高。

综上所述，甲状腺全切除术后24 h血清iPTH水平与PHP恢复时间相关，术后24 h血清iPTH水平对永久性PHP的预测价值较高，建议临床检测行甲状腺全切除术患者的血清iPTH水平，以便评估术后永久性PHP的发生风险。本研究的局限性为单中心研究，在后续的研究中还应联合多中心医院共同参与进一步的深入研究。

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