

· 论著 ·

应用国产NovoClasp系统的经导管二尖瓣缘对缘修复术 治疗原发性中重度二尖瓣反流的疗效分析

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摘要 **目的** 探讨应用国产NovoClasp系统的经导管二尖瓣缘对缘修复术治疗原发性中重度二尖瓣反流的疗效分析。**方法** 回顾分析2022年6月至2023年6月河北医科大学第一医院心脏中心应用国产NovoClasp系统进行经导管二尖瓣缘对缘修复术, 治疗并完成6个月随访的19例原发性二尖瓣反流患者的临床资料。所有患者均完善术前检查, 分析患者治疗的安全性和有效性。术后安全性相关指标包括二尖瓣夹即刻成功率、瓣夹移位、二尖瓣狭窄、心脏传导阻滞、急性心力衰竭、脑卒中、入径血管破裂、心脏压塞、术后二尖瓣反流 $\geq 2+$ 、大出血及死亡发生情况。有效性指标包括术前及术后7 d、3个月、6个月的关键心功能指标[N末端B型利钠肽前体(NT-proBNP)、可溶性生长刺激表达基因2(sST2)、左室射血分数、左心室舒张末期内径、二尖瓣反流程度、平均二尖瓣跨瓣压力阶差、二尖瓣开口面积、左心房前后径]。**结果** 治疗安全性分析结果显示, 瓣膜植入即刻成功率100%。其中, 1例应用了2枚二尖瓣夹; 1例术后发生了急性脑卒中, 为右侧顶叶及左侧顶枕叶急性脑梗死。患者均未出现瓣夹移位、二尖瓣狭窄、心脏传导阻滞、急性心力衰竭、入径血管破裂、心脏压塞、术后二尖瓣反流 $\geq 2+$ 、大出血和死亡情况。治疗有效性分析结果显示, 患者术后7 d较术前二尖瓣反流程度均显著改善($Z = 5.466, P < 0.001$)。术后临床症状改善明显, 术后7 d时, NYHA I~II级患者9例(47.4%), 与术前(1例, 5.3%)比较显著增多; 术后第6个月时 NYHA I~II级患者17例(89.5%), 显示出良好的治疗效果。术后7 d时心功能指标NT-proBNP与术前比较明显下降($P = 0.001$), 之后呈逐渐下降趋势; 术后3个月时心肌纤维化指标sST2与术前比较显著下降($P = 0.001$), 之后呈逐渐下降趋势。术后6个月时左心室舒张末期内径与术前比较差异有统计学意义($P = 0.006$)。术后7 d时平均二尖瓣跨瓣压力阶差与术前比较差异有统计学意义($P = 0.001$), 之后在术后6个月内变化不大。术后7 d时二尖瓣开口面积与术前比较差异有统计学意义($P = 0.001$), 之后在术后6个月内变化不大。术后6个月内左室射血分数、左心房前后径与术前比较差异无统计学意义($P > 0.05$)。**结论** 应用国产NovoClasp系统的经导管二尖瓣缘对缘修复术治疗原发性中重度二尖瓣反流安全、有效。

关键词 经导管二尖瓣缘对缘修复术; 原发性中重度二尖瓣反流; NovoClasp系统

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Effect of transcatheter mitral valve edge-to-edge repair using a domestic NovoClasp system for primary moderate-to-severe mitral regurgitation

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Abstract Objective To evaluate the efficacy of transcatheter mitral valve edge-to-edge repair using the domestic NovoClasp system in patients with primary moderate-to-severe mitral regurgitation (MR). **Methods** A retrospective analysis was conducted on 19 patients with primary MR who underwent transcatheter mitral valve edge-to-edge repair using the domestic NovoClasp system at the Cardiac Center, The First Hospital of Hebei Medical University, and completed a 6-month follow-up. All patients underwent a complete preoperative examination, and the safety and efficiency of surgery were evaluated. The safety indicators included immediate success rate of mitral valve clip, clip displacement, mitral stenosis, heart block, acute heart failure, stroke, access vessel rupture, cardiac tamponade, postoperative MR $\geq 2+$, major bleeding, and death. The efficiency indicators included N-terminal pro-B-type natriuretic peptide (NT-proBNP), soluble growth stimulation expressed gene 2 (sST2), left ventricular ejection fraction, left ventricular end diastolic diameter, degree of MR, mean mitral transvalvular pressure gradient, mitral valve opening area, and left atrial anteroposterior diameter at various time points (before

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surgery and at 7 days, 3 months, and 6 months after surgery). **Results** Safety indicators after surgery showed that the immediate success rate of valve implantation was 100%, including in one patient who received two mitral valve clamps and one who suffered from acute stroke (acute cerebral infarction in the right parietal lobe and left parietal-occipital lobe) after surgery. There were no cases of clamps displacement, mitral stenosis, heart block, acute heart failure, access vessel rupture, cardiac tamponade, postoperative MR $\geq 2+$, major bleeding, or death. The effectiveness indicators after surgery showed that the degree of MR significantly improved 7 days after surgery compared with that before surgery ($Z = 5.466, P < 0.001$). Clinical symptoms improved significantly after surgery, with proportion of NYHA I – II (9 cases, 47.4%) significantly higher than that before surgery (1 case, 5.3%), and 17 patients (89.5%) of NYHA I – II achieved good therapeutic effect as assessed 6 months after surgery. The level of NT-proBNP decreased significantly 7 days after surgery compared with that before surgery ($P = 0.001$); it then gradually decreased during follow-ups. sST2 significantly decreased 3 months after surgery compared with that before surgery ($P = 0.001$), with a gradually decreasing trend thereafter. The left ventricular end-diastolic diameter showed a significant difference before and 6 months after surgery ($P = 0.006$). The average mitral valve transvalvular pressure gradient was significantly different before and 7 days after surgery ($P = 0.001$), and there was little change within 6 months after surgery. The mitral valve opening area showed a significant difference before and 7 days after surgery ($P = 0.001$), with little change within 6 months after surgery. There were no significant differences in the left ventricular ejection fraction and left atrial anteroposterior diameter before and within 6 months after surgery. **Conclusion** The transcatheter mitral valve edge-to-edge repair using the domestic NovoClasp system is safe and effective for the treatment of primary moderate-to-severe MR.

Keywords transcatheter mitral valve edge-to-edge repair; primary moderate-to-severe mitral regurgitation; NovoClasp system

二尖瓣反流 (mitral regurgitation, MR) 是临床上最常见的心脏瓣膜病。我国需要临床干预的MR患者约有750万^[1]。自2003年全球开展首例应用 MitraClip 系统完成经导管二尖瓣缘对缘修复术 (transcatheter mitral valve edge-to-edge repair, TEER) 以来,截止至2021年全球TEER超过15万例^[2]。MR因病因不同分为原发性和继发性2种。原发性二尖瓣反流 (primary mitral regurgitation, PMR) 是二尖瓣本身病变引起的,多为风湿性以及退行性改变;继发性二尖瓣反流 (secondary mitral regurgitation, SMR) 是心脏或瓣膜支撑结构病变引起的^[3]。老年退行性二尖瓣反流 (degenerative mitral regurgitation, DMR) 是二尖瓣退行性病变 (包括黏液样变性) 导致的,主要表现为二尖瓣脱垂或二尖瓣腱索断裂并发连枷样病变,是最常见的 PMR^[3]。国外MitraClip系统价格较高,不适用于广大人群,因此国内急需稳定可靠的二尖瓣介入修复系统。NovoClasp系统是应脉医疗科技(上海)有限公司研发的,在其临床试验阶段(临床试验期2022年6月至2023年6月;登记编号S00504),河北医科大学第一医院心脏中心应用NovoClasp系统对19例PMR患者成功实施TEER。目前,国内尚未见相似研究报道。本研究对19例PMR患者的手术情况、术后并发症、心功能改善情况等进行了回顾性分析,探讨应用NovoClasp系统完成TEER的疗效,旨在为指导临床治疗提供依据。

1 材料与方法

1.1 临床资料

收集2022年6月至2023年6月河北医科大学第一医院心脏中心应用NovoClasp系统行TEER并完成6个月随访的19例PMR患者的临床资料。纳入标准^[4]: (1) 年龄50~75岁; (2) 依照《MR介入治疗的超声心动图评价中国专家共识》^[5]经胸超声提示中重度(3+)、重度(4+) MR; (3) 有MR相关临床症状,或无临床症状但左室射血分数 $\leq 60\%$ 或左心室收缩末期径 ≥ 40 mm; (4) 外科手术高危或无法行外科手术,且术前经TEER团队充分评估; (5) 纠治MR后的预期寿命 ≥ 12 个月。排除标准^[6]: (1) SMR; (2) 二尖瓣瓣口狭窄; (3) 无法耐受抗凝或抗血小板药物治疗; (4) 活动性感染; (5) 解剖结构不适合TEER; (6) 心腔内血栓; (7) 对药物治疗反应差的终末期心力衰竭或血流动力学不稳定且长期依赖血管活性药物或机械辅助循环支持; (8) 心肌梗死、脑梗死急性期; (9) 医学伦理委员会认为不适宜入选的患者。

本研究获得河北医科大学第一医院医学伦理委员会审查批准(研审第S00504号),所有患者自愿参加并签署知情同意书。

1.2 实施方案

河北医科大学第一医院TEER团队专家组^[6]负责19例患者全程管理,包括筛选、评估、术前准备、

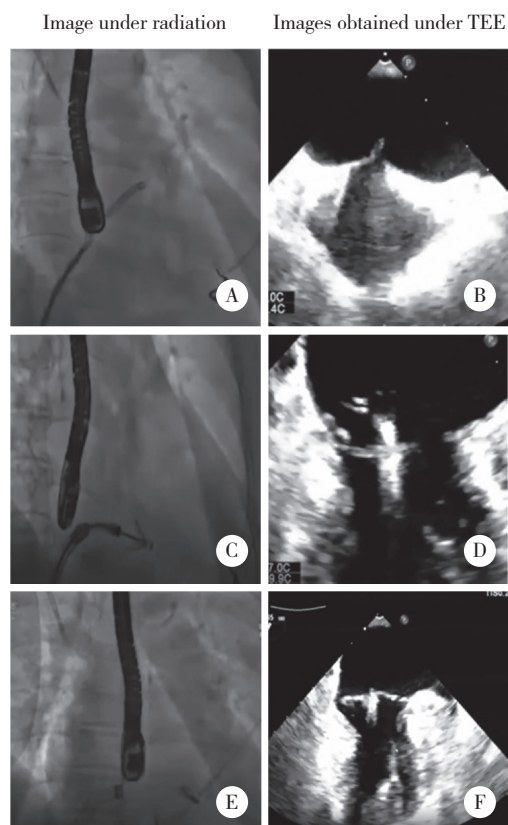
围手术期管理以及出院随访。TEER团队专家组包括心血管内科、心脏外科、心脏超声、麻醉手术团队、血管外科、心脏重症监护室、护理团队、上海应脉医疗工程师。由于TEER的特殊性,所有TEER患者的心脏超声以及复查均由心脏超声科同一位主任医师完成。

1.2.1 TEER术前管理:患者入院后均完善TEER术前常规检查,包括血常规、血生物化学、凝血、动脉血气分析、经胸超声心动图(transthoracic echocardiography, TTE)、双下肢血管超声、肺功能、经食管超声心动图(transesophageal echocardiography, TEE)、头胸CT,并给予双联抗血小板、调脂、降压、降糖等对症治疗。术前备血,并在术前24 h进行病例讨论,对病情、术式、入路、二尖瓣夹型号进行准备。

1.2.2 手术过程^[4,6-7](图1):手术在心脏专用杂交手术室进行,体外循环湿化备用,非插管全身麻醉下进行。手术采用经典经股静脉-房间隔路径,患者在超声引导下经股静脉穿刺,TEE引导下经房间隔穿刺,穿刺点位于房间隔后上方、距离二尖瓣环3.5~4.5 cm,穿刺完成后置入左心房导丝,超声引导下将22 F引导导管置入左心房,引导导管进入左心房1.0~2.0 cm,排气后将缘对缘瓣膜修复输送系统通过引导导管置入左心房,在TEE实时引导下,将瓣膜夹准确置入病变目标区域(包括调整夹子轴向,进入左心室,捕获瓣叶,关闭瓣膜夹),TEE评估瓣膜夹置入效果满意,MR减轻程度满意,无明显狭窄且瓣膜夹稳定后释放瓣膜夹,撤离输送系统,采用TEE评估手术效果。如有必要,采用同样方式置入第2枚瓣膜夹。手术完成后,撤离输送系统及引导导管,关闭股静脉穿刺口。随后TTE评估,应用压迫及外科缝合入径血管行止血,术毕送入心脏重症监护室恢复。

1.2.3 TEER术后管理^[6]:

所有患者均给予双联抗血小板[阿司匹林100 mg(1次/d)+氯吡格雷75 mg(1次/d)]治疗3~6个月,终身单药抗血小板治疗(阿司匹林100 mg/次,1次/d)^[8-10]。对于心房颤动患者,给予抗凝治疗(利伐沙班15~20 mg/次,1次/d)^[6]。另外,根据患者具体情况给予改善心力衰竭药物,包括美托洛尔、沙库巴曲缬沙坦、维立西呱、伊伐布雷定等。术后3 d严密心电监护^[6],所有患者术后7 d、3个月、6个月进行心功能指标、心脏超声复查。



A, B, performing atrial septal puncture under the guidance of TEE; C, D, insert the pericardial valve repair delivery system into the left atrium through the guiding catheter, and under the real-time guidance of TEE, accurately place the valve clip into the target area of the lesion; E, F, the TEE assessment of the valve clip placement effect is satisfactory, and the valve clip is released.

图1 应用NovoClasp系统进行TEER的重要步骤

Fig.1 Important steps of TEER using NovoClasp system

1.3 观察指标

记录治疗的安全性和有效性指标。安全性指标主要包括二尖瓣夹即刻成功率,术后瓣夹移位、二尖瓣狭窄、心脏传导阻滞、急性心力衰竭、脑卒中、入径血管破裂、心脏压塞、术后MR \geq 2+、大出血发生和死亡情况。有效性指标主要包括术前及术后7 d、3个月、6个月关键心功能指标[N末端B型利钠肽前体(N-terminal pro-B type natriuretic peptide, NT-proBNP)、可溶性生长刺激表达基因2(soluble growth stimulation expressed gene 2, sST2)、左室射血分数、左心室舒张末期内径、MR程度、平均二尖瓣跨瓣压力阶差、二尖瓣开口面积、左心房前后径]。

1.4 统计学分析

利用SPSS 23.0软件进行数据处理,符合正态分布的计量资料采用 $\bar{x} \pm s$ 表示,2组比较采用t检验。计

数资料采用率(%)表示,2组比较采用Fisher确切概率法。双侧 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者的一般临床特征

19例患者中男8例(42.1%),女11例(57.9%),年龄(79.31 ± 7.05)岁,体重指数(22.3 ± 3.6) kg/m^2 ;NYHA II级1例(5.2%),NYHA III~IV级28例(94.7%);糖尿病7例,高血压6例,冠状动脉粥样硬化性心脏病10例,心房颤动12例,完全性束支传导阻滞4例,陈旧脑梗死7例,慢性阻塞性肺疾病4例,慢性肾衰竭2例;心脑血管疾病家族史11例,吸烟5例。术前用药情况:他汀类8例(39.1%),阿司匹林7例(36.8%),氯吡格雷7例(36.8%),利伐沙班12例(63.1%), β 受体阻滞剂9例(47.3%),降糖药物7例(36.8%),利尿剂19例(100%),沙库巴曲缬沙坦钠6例(31.5%)。

其他相关临床指标包括第1秒用力呼气容积(forced expiratory volume in one second, FEV_1)为(75.4 ± 16.1)%;中重度MR(3+)7例(36.8%),重度MR(4+)12例(63.1%);二尖瓣平均对合缘高度(6.01 ± 1.34)mm,左室射血分数(54.2 ± 10.7)%,左心室舒张末期内径(58.2 ± 10.1)mm,平均二尖瓣跨瓣压力阶差(1.03 ± 0.69)mmHg,二尖瓣开口面积(5.41 ± 1.23) cm^2 ,左心房前后径(45.8 ± 6.85)mm;NT-proBNP(896.5 ± 161.8)pg/mL, sST2(73.1 ± 26.4) $\mu\text{g/mL}$,谷丙转氨酶(alanine aminotransferase, ALT)(42.2 ± 17.34)U,谷草转氨酶(aspartate aminotransferase, AST)(46.2 ± 11.43)U,血清肌酐(serum creatinine, sCr)(84.5 ± 26.71) $\mu\text{mol/L}$ 。

2.2 手术安全性分析

结果显示,瓣膜植入即刻成功率100%。其中1例应用了2枚二尖瓣夹;1例术后发生了急性脑卒中,为右侧顶叶及左侧顶枕叶急性脑梗死。所有患者均未出现瓣夹移位二尖瓣狭窄、心脏传导阻滞、急性心力衰竭、入径血管破裂、心脏压塞、术后MR $\geq 2+$ 、大出血和死亡情况。

2.3 手术有效性分析

结果显示,术后7 d患者MR无或轻度(0~1+)8例(42.1%),中度(2+)11例(57.9%),与术前比较MR程度显著改善($Z = 5.466, P < 0.001$)。术后7 d时NYHA I~II级患者9例(47.4%),第6个月NYHA I~II级患者17例(89.5%),均显著高于术前(1例,5.3%),差异均有统计学意义(均 $P < 0.05$)。心功能指标NT-proBNP呈下降趋势,术后7 d、3个月及6个月时与术前比较差异均有统计学意义(均 $P < 0.05$)。心肌纤维化指标sST2也呈下降趋势,术后临床症状改善明显,显示出良好的治疗效果;术后3个月、6个月与术前比较差异有统计学意义(均 $P < 0.05$)。左心室舒张末期内径术后6个月时显著减小,与术前比较差异有统计学意义($P = 0.006$)。平均二尖瓣跨瓣压力阶差术后7 d时显著增加,与术前比较差异有统计学意义($P = 0.001$),之后在术后6个月内变化不大。二尖瓣开口面积术后7 d时显著减小,与术前比较差异有统计学意义($P = 0.001$),之后在术后6个月内变化不大。左室射血分数、左心房前后径在术后6个月内与术前比较差异无统计学意义(均 $P > 0.05$)。见表1。

表1 患者术前,术后7 d、3个月及6个月心功能以及超声情况指标比较

Tab.1 Comparison of cardiac function and ultrasound indicators for patients before surgery and 7 days, 3 months, and 6 months after surgery

Item	Before surgery	7 d after surgery	3 months after surgery	6 months after surgery
NYHA I - II [n(%)]	1 (5.3)	9 (47.4) ¹⁾	14 (73.7) ¹⁾	17 (89.5) ¹⁾
NYHA III - IV [n(%)]	18 (94.7)	10 (52.6)	5 (26.3)	2 (10.5)
NT-proBNP (pg/mL)	876.5 \pm 162.8	410.7 \pm 241.9 ¹⁾	384.4 \pm 164.2 ¹⁾	375.6 \pm 155.4 ¹⁾
sST2 ($\mu\text{g/mL}$)	71.6 \pm 26.4	57.3 \pm 18.7	39.5 \pm 20.4 ¹⁾	40.2 \pm 18.6 ¹⁾
Left ventricular ejection fraction (%)	54.2 \pm 10.7	55.6 \pm 9.2	57.3 \pm 8.4	58.1 \pm 10.3
Left ventricular end-diastolic internal diameter (mm)	58.2 \pm 10.1	53.3 \pm 8.4	52.1 \pm 10.7	49.6 \pm 8.3 ¹⁾
Mean mitral transvalvular pressure gradient (mmHg)	1.03 \pm 0.69	2.52 \pm 1.67 ¹⁾	2.49 \pm 1.82 ¹⁾	2.56 \pm 1.77 ¹⁾
Mitral valve opening area (cm^2)	5.41 \pm 1.23	3.49 \pm 1.03 ¹⁾	3.25 \pm 1.64 ¹⁾	3.48 \pm 1.85 ¹⁾
Anterior-posterior diameter of left atrium (mm)	45.80 \pm 6.85	44.60 \pm 7.71	44.80 \pm 6.91	45.01 \pm 5.36

1) $P < 0.05$ vs. before surgery.

3 讨论

MR是最常见的心脏瓣膜病^[11],美国统计研究^[12]显示,人群中MR轻度(+)、中度(2+)、中重度(3+)及重度(4+)的发病率分别为19.2%、1.6%、0.3%及0.2%;>75岁人群中发病率接近10%。超过2/3的MR \geq 3+患者由于高龄、并发症等危险因素无法耐受手术治疗,5年内死亡率高达50%^[13]。二尖瓣复合体由前叶、后叶、腱索、乳头肌、瓣环和左心室壁组成,任一部分出现异常都会导致PMR^[14]。

多项研究^[15-18]已经证实,PMR患者中应用MitraClip系统可显著获益。除此之外,AVJ-514试验^[19]是MitraClip系统在亚洲地区PMR患者中的应用实践,手术成功率为87.5%,NYHA III~IV级患者比例从37.5%降至6.3%,没有死亡病例,术后30 d复查结果显示81.3%患者MR \leq 2+。高建斌等^[7]报道了我国自主研发的经股静脉路径缘对缘二尖瓣修复(Kokaclip™系统)的临床研究,该研究纳入了11例功能性MR患者及1例DMR患者,结果显示Kokaclip™系统具有很好的安全性及有效性,围手术期及术后30 d随访无严重器械相关不良事件,达到预期治疗结果。

本研究在19例PMR患者中应用NovoClasp系统,在TEER团队专家组负责患者全程管理下,观察术前、术中及术后的手术安全性和有效性。结果显示:(1)安全性指标良好,瓣膜植入即刻成功率100%,患者均未出现瓣夹移位、二尖瓣狭窄、心脏传导阻滞、急性心力衰竭、入径血管破裂、心脏压塞、术后MR \geq 2+、大出血及死亡情况。(2)有效性指标良好,术后7 d较术前MR程度显著改善,术后临床症状改善明显,NYHA I~II级患者比例显著高于术前,心功能指标NT-proBNP、sST2下降明显,左心室舒张末期径在术后6个月亦显著减少。可见国产NovoClasp系统在中重度(3+)、重度(4+)PMR患者中应用安全、有效,与以往相关研究结果一致。

综上所述,国产NovoClasp系统可显著改善PMR患者临床症状,效果显著。但本研究存在一定的局限性:本研究为单中心研究,样本量较小,随访时间较短,仅纳入了PMR患者;仅是对器械的可行性及安全性进行的初步验证。期待未来进行大规模医疗器械注册临床研究,为NovoClasp系统的临床应用提

供更加充分的临床证据。另外,NovoClasp系统应用效果需进行多中心、大样本、长期的随访验证。

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放射敏感性的增强作用^[11]。本研究发现,EC组织和细胞中MSI1表达水平升高,miR-625-5p直接抑制MSI1,过表达MSI1逆转了miR-625-5p对EC细胞增殖、迁移和侵袭的抑制作用,表明MSI1在EC进展中具有致癌性。

综上所述,本研究发现LINC00839可以靶向调节miR-625-5p/MSI1轴,调控EC细胞的增殖、凋亡、迁移和侵袭行为。

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