On a defective Mitraclip® system: Considerations on the medical device regulation in Europe

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Abstract

The use of medical devices is constantly growing and constitutes a valid aid to ailing people because of remarkable technological advances. The regulations on their circulation in Italy and Europe are inspired by the principle of free circulation: it is sufficient for a device to have the CE logo for it to be freely commercialized in all European countries. These regulations that favors commerce also expose the sick to the risk of harm from defective devices that have not been suitably checked prior to commercial release. This paper reports a case of a defective MitraClip® Delivery System, discusses other episodes of similar device malfunctioning, and analyzes the European legislation on medical devices. In the author's opinion, a careful "control" policy for devices, an adequate care in device manufacturing, an appropriate evaluation of pre- and post-marketing and suitable measures for the patient's safety are needed.

Introduction

The growing and unrelenting need to improve quality of life, and the will to ensure the best possible health conditions for human beings, have over the years nurtured the ever-increasing interest in medical devices, broadly defined as devices designed to be used on humans to improve their health and quality of life [1]. Furthermore, the remarkable scientific and technological advances, applied to biology, have permitted an ever-increasing number of sophisticated and inventive solutions to properly counter and overcome disablements, handicaps and pathologies that were once considered incurable.

During the last years, a new technique designed to fix mitral insufficiency via percutaneous has been developed, the MitraClip® system [2]. This system is suitable for aged patients or for those whose poor clinical conditions make surgical substitution of the mitral valve unadvisable. According to the "edge to edge" approach proposed by Alfieri [3], the two mitral edges are centrally linked by means of a metal clip, thus excluding or significantly reducing the valve regurgitation. Such a new technique represents a valid alternative to the traditional surgical approach [4] and offers good prospects for patients with cardiac failure [5]. Normally, the procedure is based on a device composed of three elements: a clip (MitraClip®), a Steerable Guide Catheter (SGC), and a Clip Delivery System (CDS). By using a transseptal catheter echo-monitored, the SGC, introduced in the femoral vein, is located in the left atrium and the CDS is shifted within the atrium. Once the devices are located within the atrium, the clip is positioned in the valve plane and its arms opened at about 180° perpendicularly to the mitral valve entrance, connected with the jet regurgitation. The clip is moved within the left ventricle, until its arms fall in correspondence to both valve edges. Subsequently, two grippers fix the edges, the clip is grasped and the edges are connected in their centre. The grasping degree and the percentage of reduction of mitral insufficiency achieved can be monitored by trans-oesophageal echography. The grasping can be repeated and other clips can be added for a better result. Once the optimal results are achieved, the clip is removed by unscrewing and withdrawing the ending knob of the thin Ametal structure by means of which the clip was insert. Then, the last security metal wire connected to the grips is removed for the complete clip release. Such a procedure is practiced daily [6], and even more papers have been published on its efficacy [7-9], the good hemodynamic functionality [10-12], the low incidence of complications or of major adverse effects [13,14], and a good subsequent quality of life [15,16]. As reported in their Guidelines, both the European Association of Cardiac Surgery and the European Society of Cardiology agree in considering the use of the MitraClip® Delivery System as a Class II B therapeutic operation for patients with severe symptomatic mitral insufficiency and at high surgical risk [17].

Recently, a case of percutaneous mitral valve repair using MitraClip® Delivery System, resulting in patient's death, has been observed and discussed here.

Case Report

A 68-year-old woman, obese (BMI = 34), hepatitis B positive, with rheumatoid arthritis and chronic renal failure, experienced asthenia and dyspnoea in December 2012. ECG highlighted an HR of 65 bpm, a

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left-sided electrical axis, intraventricular conduction at high limits, but there were no repolarization disorders. The ultrasound examination showed a severely dilated and globally hypokinetic left ventricle. The Left Ventricular Ejection Fraction (LVEF) was estimated at around 25%. The left atrium appeared to be moderately dilated. The right cavities appeared in the norm, the tricuspid and pulmonary valves without morphological alterations. As well as the mitral valve, which was described as well preserved in the absence of alterations, calcifications and thickening of the valvular and subvalvular apparatus while tethering affected both the cuspidal edges, resulting in a serious degree of insufficiency. The estimated systolic pulmonary pressure (PAPS) was 44 mmHg. Coronary arteries, with coronarography, were free of atheromatous plaques and significant stenosis.

The result of the clinical examinations, therefore, revealed for dilated cardiomyopathy with severe mitral insufficiency, associated with mild tricuspid regurgitation and the patient was classified in the fourth class NYHA. The patient underwent six months of optimal medical therapy except ACE-inhibitors due to reduce mitral insufficiency. Despite the consistent period on best medical treatment, the severe mitral regurgitation was still present. While classical surgery had too high risk (ASA 4 patient), a MitraClip procedure was planned. The surgery, monitored by both the echo and the fluoroscopy, conducted under general anaesthesia, would have allowed the correct fixing of a clip and the consequent reduction of the mitral insufficiency.

On the day of the procedure, the results of the ultrasound confirmed the effectiveness of the grasping and the success of the operation. The operator therefore decided to release the clip. During unlocking (anticlockwise rotation of the guide knob), the operator was not able to disconnect the clip from its holder due to a device failure. After several failed attempts to release the clip, it was decided to surgically remove the system. Emergency surgery was performed in the extracorporeal circulation, aortic clamping and cardioplegia, a percutaneous procedure was performed according to Alfieri [3], completed with valve plastic. After surgery, the patient showed a left ventricular dysfunction (VF). After defibrillation, sinus rhythm was supported by inotropic drugs, with BP 110/60, HR 100 bpm and EF 30%. The patient was transferred to intensive care, where she was hit by bilateral pneumonia and endocarditis. Although the MitraClip® implant and overall cardiac procedures had been performed correctly, the patient died 20 days after surgery due to septic shock.

Discussion

The MitraClip® Delivery System, although defective in the presented case, passed all quality controls required by European legislation, bore the CE mark, and has been successfully applied several times. It passed two randomized studies (Everest I and Everest II), It has been shown to be a full-scale study of the mitral valve that could be performed in full security, with a low rate of morbidity and mortality and satisfactory follow-up. Both the randomized [18-20] and a further 43 studies on 6865 patients [17] showed neither malfunction nor mortality after device use. Following commercialization of the MitraClip® Delivery System, cases of malfunctioning of the device, due to failure in clip detachment, were reported. After nine cases of malfunctioning, followed by severe comorbidity and complications, with one patients' decease - as in this case - the company recalled the MitraClip® Delivery System manufactured from July 14, 2015 to August 11, 2015 and distributed from August 28, 2015 to February 3, 2016 [21]. Moreover, the Company provided further instructions and training for health care providers who use the device, detailing contraindications and complications for device use [22]. In particular, potential complications were related to general clinical manifestations, to cardiac complications and device migration or malposition. Post-surgical pneumonia and endocarditis, commonly occurring in patients undergoing emergency open heart surgery and presenting high risks (ASA IV and NYHA IV).

An analogous device, Lotus Valve System, although positive clinical outcomes [23,24], has evidenced a similar problem. In particular, the Lotus Valve becomes unlocked, with the need to convert the patient to surgery. FDA established a class I recall, involving 278 units distributed all over European countries [25].

The specialized literature reported several cases of defective cardiac devices. In 2003, Bottio and coll. reported a case of defective cardiac valve in Italy, in which the pivot of the metal disk would often break, putting the patient's life into serious danger. In particular, 5 out of 36 patients died, while in 12 patients, the valve had to be removed and replaced [26]. Other cases of defective valves were reported [27]. Thereafter, the less than perfect "integrity" of aortal endo-prostheses two to the use of unsuitable materials was reported [28].

Several devices applied in different organs and / or tissue, presented defects after commercialization [29-34], highlighting the need for accurate post-marketing surveillance.

The potential hazards of devices induced the European [35] and Italian [36] legislators to issue a considerable number of laws aimed to ensure mandatory safety standards and performance concerning design, building, materials' choice and absence of harmful substances, while assuring free circulation after clinical investigations on the European market of devices that comply with such characteristics [37]. The corresponding certification, confirming the attainment of the specified criteria through a specific symbol (CE), is awarded by an Independent Organization (Notified Body) monitored by the National Authority [38]. The Notify Body, releasing the CE mark, has to receive all available clinical and data, as well as those reported in literature, a declaration on the employment of allowed materials and on the absence of dangerous ones.

Summarizing, the European regulation [1,35,36] states that the Manufacturers have to:

- define the particular class of the device;
- meet with minimal requirements;
- publish a compliance statement;
- present adequate clinical data;
- introduce the compliance scheme evaluation.

Upon reception, the Notified Body verifies them and decides about the CE mark release. Despite these procedures, it must be kept in mind, as pre-marketing studies are not always able to highlight eventual, possible device deficits. A specific European Directive [39] states the need of performing an accurate post-marketing surveillance when the device is used in common clinical practices. Such a solution, while doubtlessly much appreciated by the industrial world, since devices' commercialization times are noticeably shortened, does not seem adequate for a complete patient guarantee. Consequently, the application of a device does not always offer the expected benefits, as demonstrated by several literature cases [40,41], as well as the one discussed here.

Although device malfunctioning is a remote occurrence, much disappointment is aroused because of the possible serious risk for the health and the life of the patient and necessarily leads to considerations on the need of suitable, proper checks in devices' planning, manufacturing and clinical investigation pre- and post-marketing [42,43].

In summary, the CE mark does not imply absolute efficiency of the devices [44,45], and the Italian Courts repeatedly invoked the responsibility of both Manufacturers and Certification Body [46], while physician responsibility can be invoked only in regards to errors in clinical indications and device application. Freemantle states the current Euro-

pean legislation for medical devices seems to be inadequate to assure a sufficient safeguard for patients and their quality of life [47].

Conversely, in the US, where the National Authority [48] ensures a severe premarketing control, the FDA must declare the reasonable assurance of safety and effectiveness of devices before authorizing their commercialization [49,50]. During last years, only 2% of devices undergoing evaluation obtained FDA approval [51]. Such approach seems more appropriate to safeguard both the patients' lives and quality of life. Nevertheless, the process is rigid, lengthy and costly without granting an absolute certainty for patients' safety.

Conclusions

The here reported case highlights all the vulnerability of the European certification system. In our opinion, this system could be greatly improved by simply avoiding the possibility for Manufacturers to choose the Notification Body for CE mark, as well as establishing uniform operative standards to be accomplished by all European Notification Bodies. Moreover, it would be advisable to pay great attention not only to a device's safety, but also in its effectiveness, with particular care for cardiovascular devices. Comprehensive information about the premarketing studies, including trial results, should be accessible on-line; before authorizing a new device commercialization, randomized studies aimed to verify their safety and effectiveness with respect to similar devices already available on the market should be performed. A conditional approval, for a limited time interval, should be released in those situations when clinical data are insufficient or without clear clinical benefits; the post-marketing surveillance should be periodically updated (every three years) by Manufacturers and Clinicians as well as by stakeholders, also contemplating the possible withdrawal of the device from the market.

An adequate device monitoring, especially for cardiac and other high-risk devices [52-56], based on use of National databases, on specific applications, allowing a quick and effective action in case of malfunctioning, must be considered. A recent analysis about the transcatheter aortic valve implantation (T.A.V.I.) demonstrated, in fact, that 20-25% of them exceeded the clinical evidence [57]. Although the possibility of commercialization of defective or scarcely efficient devices cannot be avoided entirely, the proposed modification can, in our opinion, significantly contribute in improving the system.

Although relevant, the scientific and economic interests related to the device's production and commercialization cannot prevail on the need of public health's protection: scientific and technological progress has to marry patients' safety and health care, without considering the relevant profits. Such aspect represents the new challenge in favour of patients and society.

References

1. European Commission. Guideline 2007/47/CE of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market.
2. Condado JA, Acquatella H, Rodriguez L. Percutaneous edge to edge mitral valve repair: 2 years follow-up in the first human case. Catheter Cardiovasc Interv 2006;67:323-5.
3. Alfieri O, Maisano F, De Bonis M. The double orifice technique in mitral valve repair: a simple solution for complex problem. J Thorac Cardiovasc Surg 2001;122:674-81.
4. Ussia GP, Camalleri V, Scandura S, Tamburino C. Correzione percutanea dell'insufficienza mitralica: un nuovo strumento nell'armamentario per lo scompenso cardiaco? G Ital Cardiol 2012;13:356-65.
5. Denti P, Alfieri O. Chirurgia mitralica per via percutanea. Attualità e prospettive. Cardiology Sci 2013;11:58-9.
6. Scandura S, Camalleri V, Pistritto AM, et al. Riparazione percutanea della valvola mitralica: indicazioni, risultati e limiti. Cardiology Sci 2012;10:266-73.
7. Argentano M, Skipper E, Heimansohn D. Surgical revision after percutaneous mitral repair with the MitraClip device. Ann Thorac Surg 2010;89:72-80.
8. Feldman T, Foster E, Glower. DD. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395-406.
9. Goldberg SU, Feldman T. Percutaneous mitral valve interventions: overview of new approaches. Curr Cardiol Rep 2010;12:404-12.
10. Hermann HC, Rohatgi S, Wasserman HS. Mitral valve hemodynamic effects of percutaneous edge to edge repair wuth the Mitraclip device for mitral regurgitation. Catheter Cardiovasc Interv 2006;68:821-8.
11. Siegel RJ, Biner S, Rafique AM. The acute hemodynamic effects of MitraClip therapy. J Am Coll Cardiol 2011;57:1658-65.
12. Turi ZJ, Rosenbloom M. An option for the high-comorbidity patient with mitral regurgitation. J Am Coll Cardiol 2012;59:140-2.
13. Franzen O, Van der Heiden J, Baldus S. Mitraclip therapy in patients with end-stage systolic heart failure. Eur J Heart Fail 2011;13:569-76.
14. Tamburino C, Ussia GP, Maisano F. Percutaneous mitral valve repair with the Mitraclip system: acute result from a real world setting. Eur Heart J 2010;31:1382-9.
15. Ussia GP, Cammalleri V, Darkar K. Quality of life following percutaneous mitral valve repair with the Mitraclip System. Int J Cardiol 2012;155:194-200.
16. Tan MKA, Jarral OA, Thong EHE, et al. Quality of life after mitral valve intervention. Interact Cardiovasc Thorac Surg 2017;24:265-72.
17. Vahanian A, Alfieri O, Andreotti F. Guidelines on the management of valvular heart disease (version 2012): The joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1-44.
18. Feldman T, Wasserman HS, Hermann HC. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Fhase I Clinical Trial. J Am Coll Cardiol 2005;46:2134-40.
19. Feldman T, Kar S, Rinaldi M. Percutaneous mitral repair with the MitraClip System: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) cohort. J Am Coll Cardiol 2009;54:686-94.
20. Feldman T, Foster E, Glower DD. EVEREST II Investigators Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395-406.
21. U.S. Food and Drug Administration. Abbott Vascular MitraClip recall. Available from: https://www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm490774.htm
22. MitraClip® NT delivery system. Indication for use. AP2939260-WBU Rev. D. Abbott. August 2017, available at: https://www.vascular.abbott/us/products/structural-heart/mitraclip-mitral-valve-repair.html
23. U.S. Food and Drug Administration. Class I device recall Lotus Valve System. FDA recall number: Z-0915-2015. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=131993
24. Meredith IT, Walters DL, Dumonteil N, et al. 1-year outcomes with the fully repositionable and retrievable lotus transcatheter aortic replacement valve in 120 high-risk surgical patients with severe

aortic stenosis: Results of the REPRISE II study. JACC Cardiovasc Interv 2016;9:376-384
25. De Backer O, Götberg M, Ihlberg L, et al. Efficacy and safety of the Lotus Valve System for treatment of patients with severe aortic valve stenosis and intermediate surgical risk: Results from the Nordic Lotus-TAVR registry. Int J Cardiol. 2016;219:92-97.
26. Bottio T, Casarotto D, Thiene G, et al. Leaflet escape in a new bileaflet mechanical valve TRI technologies. Circulation 2003;13:1-4.
27. Hansen L, Danne M, Hoffmann B, Riess FC. Structural valve failure -with every beat regurgitation observed using the Medtronic Advantage aortic valve. J Thorac Cardiovasc Surg 2007;134:1344-5.
28. Veith FJ, Baum RA, Ohki T. Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. J Vasc Surg 2002;35:1029-35.
29. Mattova J, Bahacava F, Murgasova Z. Opacification of hydrophilic Memorylens U940A intraocular: analysis of 2 explanted lenses. J Cataract Refract Surg 2004;30:193-9.
30. Torre M. Polietilene ad elevato peso molecolare per protesi ortopediche. Sterilizzazione, degrado e usura. Notiziario dell'Istituto Superiore di Sanità 2005;18:3-8.
31. Italian Ministry of Health, Department of Innovations, General Direction of Drugs and Medical Devices. Nota riguardante i componenti di protesi ortopediche impiantabili contenenti polietilene ad altissimo peso molecolare (UHMWPE). 2005.
32. Langton DS, Sidaginamale RP, Avery P, et al. Retrospective cohort study of the performance of the Pinnacle metal on metal (MoM) total hip replacement: a single-centre investigation in combination with the findings of a national retrieval centre. Br Med J Open 2016;6:e007847.
33. Williams GM, Caldwell J, Armstrong D, et al. Multicenter study to assess potential hazards from exposure to lipid peroxidation products in soya bean oil from Trilucent breast implants. Regul Toxicol Pharmacol 2009;53:107-20.
34. Italian Ministry of Health. Law 5 June 2012, no. 86. Refer to: "Opinion of the Board of Health", 22 December 2011 and 29 December 2011.
35. European Commission. Directive 90/385/CEE, Directive 93/42/CEE, Directive 2003/12/CE, Directive 2003/32/CE, Directive 2003/50/CE, Directive 2007/47/CE.
36. Italian Ministry of Health. Decrees: 23 July 1998; 10 October 2001; 3 February 2003; 5 August 2005; 15 November 2005; 20 February 2007; 12 March 2013; 25 June 2014. Laws: 23 December 2005 no. 266; 27 December 2006 no. 296; 25 January 2010 no. 37.
37. Italian Ministry of Health. General Management of Pharmaceuticals and Medical Devices: "Dispositivi medici (aspetti regolatori e operativi)", 2007; "Le indagini cliniche dei dispositive medici", 2015.
38. European Commission. Legislative decree 507/92/CE (Attachment 8); legislative decree 46/97 (Attachment XI).
39. European Commission. Guideline Meddev 2.7/3. Clinical investigations: serious adverse event reporting under directives 90/385/EEC and 93/42/EEC, 2010.
40. Heneghan C. The saga of Poly Implant Prothèse breast implants. Br Med J 2011;344:e306.
41. Di Mario C, James S, Dudek D, et al. Commentary: The risk of over-regulation. Br Med J 2011;342:d3021.
42. Vacchiano G. L'utilizzo dei dispositivi medici tra obblighi normativi, difficoltà operative e possibili responsabilità. Proceedings Nat. GISDI Congr., Macerata, Italy, 2008:81-101.
43. Mongillo R, Vacchiano V. OS dispositivos medicos e a marca "CE". Lex Medicinae 2009;11:57-66.
44. Bonelli A, De Luca F. Aspetti normativi e medico legali in tema di usabilità di dispositivi medici. Riv Ital Med Leg 2013;3:1259-69.
45. Bugiolacchi L. Sicurezza dei prodotti e certificazione: la responsabilità contrattuale degli organismi di valutazione della conformità. Respons Civ Prev 2013;2:610-26.
46. Cassazione Civile Sez. III Sentenza 20 Luglio 1993 n. 8069; Corte di Cassazione, Sez. Unite, Sentenza n. 13533 del 30 Ottobre 2001. Tribunale di Monza 4 Febbraio 2004; Cassazione Civile Sez. III Sentenza 8 Ottobre 2007 n. 20985; Cassazione Penale sez. VI, Sentenza 4 maggio 2011, n. 40897, CED Cassazione Penale, 2011; Tribunale di Piacenza 3 Maggio 2012, in Resp Civ Prev 2013;2:604.
47. Freemantle N. Evaluating and regulating the device industry. Br Med J 2011;342:d2839.
48. Sorenson C, Drummond M. Improving medical device regulation: The United States and Europe perspective. Milbank Q 2014;92:114-50.
49. US Government Accountability Office. Classes of Devices. Washington, DC: US Government Printing Office. Publication n. 21 USC 360; 2006.
50. US Food and Drug Administration. Device advice: premarket notification. Rockville: 2000.
51. Sweet BV, Schwemm AK, Parsons DM. Review of the processes for FDA oversight of drugs, medical devices, and combination products. J Mange Care Pharm 2011;17:40-50.
52. Vacchiano G, Vyshka G. Severe flaccid paraparesis following spinal anaesthesia: a sine materia occurrence. BMJ Case Rep 2014;5:1757-90.
53. Vacchiano G, Vyshka G. Balkans syndrome: A potential link between multiple sclerosis and hypervaccination. J R Army Med Corps 2012;158:338-40.
54. De Robertis E, Ricci S, Pieri M, et al. Cerebral sinus thrombosis after spinal anaesthesia: predisposing factors, operating difficulties and diagnostic problems. EuroMed Biomed J 2017;12:159-62.
55. Vacchiano G, Tecchia LB, Tortora F, et al. Spinal epidural hematoma following cardio aortic surgery: Any correlation possible? Acta Med Mediterr 2017;6:1163-9.
56. Vacchiano G, Rocca A, Compagna R, et al. Transurethral resection of the prostate, bladder explosion and hyponatremic encephalopathy: A rare case report of malpractice. Open Med 2017;1:50-7.
57. Van Brahandt H, Neyt M, Hulstaert F. Transcatheter aortic value implantation (TAVI): risky and costly. BMJ 2012;345:e4710.