



DOI: <https://doi.org/10.5554/22562087.e1035>

The addition of Tirofiban infusion to heparin for intraoperative heparin resistance associated with Marfan Syndrome

Adición de una infusión de Tirofiban a heparina en caso de resistencia intraoperatoria a la heparina asociada al Síndrome de Marfan

Maria José Fernandez-Turizo^a , David Benavidez-Zora^b , Augusto Enrique Anaya-Hoyos^c, Sebastian Portillo-Gómez^b, Hernán Darío Castro-Arias^{b,d}

^a Clínica El Rosario. Medellín, Colombia.

^b Clínica Medellín Grupo Quironsalud. Medellín, Colombia.

^c Clínica las Américas. Medellín, Colombia.

^d Programa de Anestesiología Cardiovascular, Universidad CES. Medellín, Colombia.

Correspondence: Calle 20 No. 2 sur-185. Clínica El Rosario. Medellín, Colombia.

How to cite this article: Fernandez-Turizo MJ, Benavidez-Zora D, Anaya-Hoyos AE, Portillo-Gómez S, Castro-Arias HD. The addition of Tirofiban infusion to heparin for intraoperative heparin resistance associated with Marfan Syndrome. Colombian Journal of Anesthesiology. 2022;50:e1035.

Email: marijfdz@hotmail.com

Abstract

Marfan syndrome classically presents with aortic root aneurysms. Aortic ectasia causes diverse blood flow alterations, influencing the behavior of coagulation factors and platelet activity. Heparin resistance has also been reported associated with Marfan Syndrome in a small number of patients, probably due to antithrombin III (ATIII) deficiency or various mutations. The ascending aorta and the aortic valve are replaced with prosthetic material during Bentall- de Bonno procedures. Resistance to anticoagulation during extracorporeal circulation, represents a significant challenge for both anesthesiologists and the surgical team. Resistance to heparin was observed in a patient with Marfan syndrome undergoing a Bentall procedure. ATIII concentrate was not available, and Activated Coagulation Time did not increase despite high doses of heparin. An alternate anticoagulation approach was used successfully.

Key words: Cardiopulmonary bypass; Heparin, Resistance; Antithrombin III Deficiency; Anticoagulation; Platelet Aggregation Inhibitors; Anesthesiology.

Resumen

El síndrome de Marfan clásicamente se presenta con aneurismas de la raíz de la aorta. La ectasia aórtica produce alteraciones en el flujo sanguíneo que influyen sobre el comportamiento de los factores de la coagulación y la actividad de las plaquetas. También se ha reportado resistencia a la heparina asociada al Síndrome de Marfan en un menor número de pacientes, probablemente debido a deficiencia de antitrombina III (ATIII) o a diversas mutaciones. La aorta ascendente y la válvula aórtica se reemplazan con material protésico en los procedimientos Bentall- de Bonno. La resistencia a la anticoagulación durante circulación extracorpórea significa un enorme desafío tanto para los anestesiólogos, como para el equipo quirúrgico. Se observó resistencia a la heparina en un paciente con Síndrome de Marfan sometido a un procedimiento de Bentall. No había disponibilidad de concentrado ATIII y no aumentó el ACT (Tiempo de Coagulación Activada) a pesar de las elevadas dosis de heparina. Se utilizó exitosamente un abordaje alterno de anticoagulación.

Palabras clave: Bypass cardiopulmonar; Heparina, Resistencia; Deficiencia de Antitrombina III; Anticoagulación; Inhibidores de la agregación plaquetaria; Anestesiología.

Lea la versión en español de este artículo en www.revcolanest.com.co

Copyright © 2022 Sociedad Colombiana de Anestesiología y Reanimación (S.C.A.R.E.).

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

CASE REPORT

A 24-year-old man with a history of Marfan Syndrome presented to the hospital with a 55 mm aneurysm of the ascending aorta extending into the aortic arch. The diagnosis was confirmed by CT angiography and surgical correction using the Bentall- de Bono procedure was planned. Preoperative laboratory tests included an elevated serum creatinine of 2.3 mg/dl. The rest of the values were unremarkable, including platelet count, PT, PTT, and fibrinogen level. The patient weighs 46 kg and is 1.94 meters tall.

The intraoperative assessment included continuous electrocardiographic monitoring, oximetry, and non- invasive blood pressure measurement. After preoxygenation, the induction of anesthesia was performed with midazolam 10 mg IV, fentanyl 500 mcg IV and pancuronium bromide 8 mg IV. Under general anesthesia, central venous catheters (CVC) were inserted via the right internal jugular vein and the left femoral artery for invasive blood pressure monitoring. Anesthesia was maintained with isoflurane and 100% oxygen to achieve a 1 MAC. Following sternotomy 13,800 U (300 U/kg) of heparin sodium Fresenius solution 5 000 U/5 ml was injected via CVC, before aortic cannulation. Activated Coagulation Time (ACT) was measured with the device ACT Plus® Automated Coagulation Timer. Medtronic, Minneapolis, MN, USA. The baseline measurement was 131 seconds (used to construct the ACT-heparin Curve). **Table 1** shows the coagulation profile of the case discussed. 4 minutes after heparin administration ACT was 331 seconds. An additional 5000 U dose of heparin was administered, for a total of 18,800 U (408 U/kg). ACT was 287 seconds after the additional dose.

Since the preoperative lab results were within the normal limits, the possibility of ATIII deficiency was suspected. Due to the non-availability of ATIII concentrate in the institution, 3 units of FFP were administered via CVC in addition to the use of extracorporeal circulation. Each FFP bag was 250 ml and ATIII concentrations ranged between 92-129 U. Meanwhile alternate

TABLE 1. Anticoagulation profile of the study patient.

Time	ACT (Seconds)	Heparin given (U)	Total heparin (U/kg)-	Temperature (°C)	Protamine (mg)	Comments
09:15	131			37.1		Basal
10:10		13,800	300			
10:15	331	5,000	108			
10:20	287			36.2		
10:25	298					
11:10	262					3 U of FFP
11:38	350	7,500				
12:00	310	5,000	271	35		Tirofiban 10mcg/kg IV bolus 0.15mcg/kg/min IV infusion
12:05	425					CPB on
12:20	485					
13:00	435					
13:30	425		35			
14:00	430					Tirofiban stopped
14:30	305	10,000	217			
15:00	318			36.8		
15:10				37.2	250	CBP off
15:45	133		900	36.5		End of the procedure

ACT: Activated Coagulation Time; CPB: Cardiopulmonary bypass; FFP: Fresh Frozen Plasma.

SOURCE: Authors.

heparin vials were used, to avoid storage or manufacturing errors. 7500 U of heparin were administered with the FFP, and 5000 U were added to the previous dose. The total accumulated dose of heparin at the time was 31,300 U (271 U/kg) and ACT measurement was 350 seconds.

Creatinine was elevated, therefore bivalirudin which is the most frequently used agent and a proven alternative to heparin, was not considered. No thrombin inhibitors with an optimal profile in renal dysfunction were available. A prompt decision was made to start another anticoagulation alternative and the surgical team administered tirofiban, based on the successful evidence of

multiple patients involved in the studies performed by Koster et al. and additional evidence in patients with HIT and renal dysfunction. No successful experiences have been reported with different anti platelet medications. Tirofiban effectively delays thrombin generation and prolongs ACT in heparinized blood.

Since the team had no experience with tirofiban, they followed a published protocol called RESTORE, considering the risk of significant thrombosis of the extracorporeal circulation circuit. A 10 mcg/kg bolus, followed by a 0.15 mcg/kg/min infusion was used. Platelet function and blood-based point-of-care testing were not available during intraoperative

tirofiban infusion, but platelet count was normal. ACT was used as an alternative to monitor the coagulation profile for achieving a successful CPB, pursuant to the scientific evidence available from in vitro studies and articles published by Koster et al. After obtaining an ACT value of 425 seconds, the surgical team decided to start cardiopulmonary bypass. Standard blood cardioplegia was used, with no evidence of clot formation during the procedure. The ACT measurement taken 15 minutes after the administration of tirofiban was 485 seconds. The infusion was maintained for 60 minutes, strictly following the RESTORE protocol; the ACT measurements were all above 400 seconds.

After discontinuing the tirofiban infusion, ACT fluctuated over the course of the CPB; however, tirofiban was not reinitiated because the RESTORE protocol was suspended 60 minutes before the extracorporeal circulation was stopped and the surgical team did not want to take additional risks. Therefore, an additional heparin dose of 10,000 U (217 U/Kg) (900 U/kg total accumulated dose) was administered, for a total of 41,300 U (900 U/kg accumulated dose). The Bentall- de Bono procedure was successfully completed and a SJM TM Master Series Aortic Valved Graft 29 was inserted. Extracorporeal circulation was maintained uneventfully for a total of 185 minutes. At the end of the procedure 250 mg of protamine were used to neutralize heparin. This dose was calculated using the dose-response curve protocols. The last ACT measurement was 133 seconds. Hemostasis was ensured after the procedure and postoperative drainage was 370 ml on the first postoperative day and 160 ml on the second day. Following the procedure, the patient has been on warfarin without complications.

DISCUSSION

Marfan syndrome is an autosomic dominant disease frequently associated with an FBN1 gene mutation in the

15q21 chromosome. Mutations coding for fibrillin protein cause aneurysmal malformations of the ascending aorta and the aortic arch. Additional manifestations include aneurysms in distal portions of the aorta and valvular abnormalities. The aneurysmal deformation of the aorta alters blood rheology and prevents laminar blood flow, leading to hemostatic abnormalities (1).

Shear stress and flow turbulence are increased due to valvular abnormalities and vascular changes present in patients with Marfan Syndrome (2-4). In addition to physiologic blood flow anomalies, some disruptions are also present in the behavior of both coagulation factors and platelets, as well as hemostasis, platelet activation, fibrinolysis, and intercellular interactions (5-7). A cross-sectional case-control study by Kornhuber et al. included 51 patients with genetically proven Marfan syndrome and 50 healthy individuals in the control group. The study found a statistically significant reduction of Von Willebrand Factor (VWF), Factor VIII activity and prolonged D-dimer, PFA Col/ADP test, and Partial Thromboplastin time. VWF-acquired abnormalities were both qualitative and quantitative, characteristic of VWF syndrome type 2A. Evidence supporting a qualitative platelet activity abnormality was also found in these patients with altered PFA 100 tests (1).

Preventing thrombosis while using an extracorporeal circulation circuit is critically important. Heparin has been used as the first option for anticoagulation during cardiac surgery due to the availability of the antidote protamine, and the ACT test for monitoring its effect. Heparin resistance has been defined as the use of more than 35,000 UI/day of heparin. The ACT target value is controversial; however, general recommendations establish > 400 seconds as a safe parameter (7-13). It is important to recognize factors that may alter the ACT indirectly or directly. Hypothermia, antiphospholipid antibodies, inflammation, sepsis, hemodilution, previous heparin, direct thrombin and platelet inhibitors, warfarin use and factor deficiencies have

all been associated to heparin resistance. Additionally, heparin resistance has been strongly associated with antithrombin III (ATIII) and factor VIII deficiencies (7,13).

Heparin resistance in 3 patients with Marfan Syndrome was reported by Choudhury et al (14). The association is suspected to be related either to ATIII deficiency or point mutations leading to a dysfunctional molecule (7, 13-14). When heparin resistance is suspected, current evidence from various clinical trials suggests that the supplementation of purified or recombinant ATIII during CPB is effective in restoring responsiveness to heparin and increasing ACT. Additionally, FFP is an option when ATIII supplementation is not feasible (13,15). Other strategies when heparin resistance is suspected while using CPB include the use of supraphysiologic doses of heparin and seeking alternative anticoagulation options. Currently, thrombin inhibitors are the most often used options. However, there is yet no valid alternative available, and the use of thrombin inhibitors derives from expert recommendations (15).

This case discusses a patient with suspected heparin resistance due to ATIII deficiency and no heparin responsiveness with supraphysiologic doses of heparin and administration of FFP. ATIII was not available, hence high doses of heparin were initially used. ACT remained below the target (> 400 seconds) and alternative anticoagulation with tirofiban was considered in a scenario in which bivalirudin was not a suitable option due to the elevated creatinine level and additional thrombin inhibitors were unavailable. Tirofiban and other platelet inhibitors have been considered during CPB in the presence of Heparin-Induced Thrombocytopenia (HIT) and severe renal dysfunction (7,11,16-19). Koster et al published three studies regarding the use of Tirofiban during CPB (17-19). Tirofiban was used according to the RESTORE protocol in a series of 10 patients, in which an initial bolus of 10 micrograms/kg and a continuous infusion of 0.15 microgram/kg/min were administered.

The study established a target ACT of 480 seconds. Standard doses and additional boluses of heparin were used to achieve this target and the tirofiban infusion was discontinued 60 minutes before the end of the CPB. In the original protocol, the anticoagulant effect was monitored with ACT, platelet aggregometry and thromboelastography. The postoperative evaluation of the circuit found no thrombus formation and no additional complications or significant blood loss (17).

Koster et al. found that effective GP IIB/IIIa inhibition decreases hemostatic activation and inflammation induced by cardiac surgery involving a cardiopulmonary bypass. These data are from a large number of patients followed over 3 years and various types of exposures. Platelets release multiple inflammatory cytokines that promote leukocyte adhesion and migration. Tirofiban-like medications in addition to heparins may decrease fibrin micro emboli in post cardiopulmonary bypass ischemic injury and cognitive impairment (19). Moreover, Tanaka et al studied the in vitro effects of tirofiban on hemostasis in cardiac surgery patients, assessing thrombin formation and the degree of platelet inhibition. Additionally, the interaction of tirofiban and heparin on clot formation was also evaluated with ACT. The results showed that the addition of Tirofiban delayed the onset of thrombin generation triggered by adenosine diphosphate (ADP), and subsequent clot formation. Heparin delayed the onset and the rate of fibrin formation, which was further slowed down upon the addition of tirofiban to heparin (20-22).

Both platelet function tests and ACT have been reported as feasible options for CBP monitoring with the platelet inhibitor tirofiban (17-19). In the study performed by Tanaka et al. ACT levels were significantly higher when tirofiban was added to previous heparin, regardless of the level of heparin. ACT was significantly increased with tirofiban as compared against heparin alone or even heparin plus ATIII concentrate (22). The TARGET study published in 2004,

compared ACT levels in two different groups, tirofiban+ heparin and abciximab+ heparin. Both groups had a similar increase in ACT levels, with no statistically significant group difference (23). In addition, ACT used during CPB must be interpreted as a measure of both platelet coagulation activity and heparin activity (24).

These studies show that Tirofiban is an adequate option for anticoagulation in patients with renal dysfunction and an alternative strategy during CBP. Nevertheless, 3 cases of severe bleeding refractory to platelet transfusions in association with tirofiban, led the manufacturer to prevent clinicians from using tirofiban during CPB (20-21).

Further studies are warranted to make a final recommendation on the use of Tirofiban during CPB due to the available controversial evidence. An optimal dosing regimen, as well as an adequate form of intraoperative monitoring should be established. The need for immediate antithrombotic therapy following surgery should also be defined. Anesthesiologists and members of the surgical team need to be prepared in cases of heparin resistance and when additional complications with anticoagulation arise; hence, alternative anticoagulation options should be sought.

CONCLUSION

Marfan Syndrome represents a challenge for clinicians due to the presence of multiple physiologic and hematologic alterations, including heparin resistance. Effective anticoagulation is of vital importance during cardiovascular surgery and optimal management of heparin resistance is under study. Based on the available evidence, supplementation with ATIII is the ideal approach for initial management. However, there is no widespread availability of ATIII and FFP is not always effective. Furthermore, heparin resistance is associated with multiple other factors. This highlights

the importance of undertaking large multicenter studies to determine the adequate management of heparin resistance and assess the potential of alternative antithrombotic therapies.

ETHICAL DISCLOSURES

Ethics committee approval

This study was approved by the Clínica Imbanaco Research Ethics Committee, in a meeting held on June 24 2021, as recorded in act number IRB00008539. The recollection of the information was retrospective, it did not pose any risk whatsoever for the patients. Confidentiality was guaranteed by using identity masking during the analysis process.

Protection of people and animals

The authors declare that no experiments have been performed on humans or animals for this research. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Data Confidentiality

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent

The authors declare that no patient data appear in this article. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

AUTHOR CONTRIBUTION

MJFT and DBZ: wrote the manuscript.

AEAH and HDCA: obtained the lab work and data for the case.

AEAH, SPG and HDCA: edited and finalized the manuscript.

Assistance for the study

No additional assistance was received for the elaboration of this manuscript.

Funding

No funding was required or received for the elaboration of this research project and manuscript.

Conflicts of Interest

The authors do not have any relevant conflicts of interest to report.

Presentations

This manuscript and abstract have not been presented elsewhere.

Appreciations

None declared.

REFERENCES

- Kornhuber K, Seidel H, Pujol C, Meierhofer C, Rösenthaller F, Pressler A et al. Hemostatic abnormalities in adult patients with Marfan syndrome. *Cardiovasc Diagn Ther.* 2019;9(S2):S209-20. doi: <https://doi.org/10.21037/cdt.2019.08.09>
- Bogren H, Mohiaddin R, Yang G, Kilner P, Firmin D. Magnetic resonance velocity vector mapping of blood flow in thoracic aortic aneurysms and grafts. *J Thorac Cardiovasc Surg.* 1995;110(3):704-14. doi: [https://doi.org/10.1016/S0022-5223\(95\)70102-8](https://doi.org/10.1016/S0022-5223(95)70102-8)
- Geiger J, Markl M, Herzer L, Hirtler D, Loeffelbein F, Stiller B et al. Aortic flow patterns in patients with Marfan syndrome assessed by flow-sensitive four-dimensional MRI. *J Magn Reson Imaging.* 2011;35(3):594-600. doi: <https://doi.org/10.1002/jmri.23500>
- Bellini C, Korneva A, Zilberberg L, Ramirez F, Rifkin D, Humphrey J. Differential ascending and descending aortic mechanics parallel aneurysmal propensity in a mouse model of Marfan syndrome. *J Biomechanics.* 2016;49(12):2383-9. doi: <https://doi.org/10.1016/j.jbiomech.2015.11.059>
- Hathcock J. Flow Effects on Coagulation and Thrombosis. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2006;26(8):1729-37. doi: <https://doi.org/10.1161/01.ATV.0000229658.76797.30>
- Gogia S, Neelamegham S. Role of fluid shear stress in regulating VWF structure, function and related blood disorders. *Biorheology.* 2016;52(5-6):319-35. doi: <https://doi.org/10.3233/BIR-15061>
- Finley A, Greenberg C. Heparin Sensitivity and Resistance. *Anesthesia & Analgesia.* 2013;116(6):1210-22. doi: <https://doi.org/10.1213/ANE.0b013e31827e4e62>
- FitzGerald D, Patel A, Body S, Garvin S. The relationship between heparin level and activated clotting time in the adult cardiac surgery population. *Perfusion.* 2009;24(2):93-6. doi: <https://doi.org/10.1177/0267659109106729>
- Bull B, Korpman R, Huse W, Briggs B. Heparin therapy during extracorporeal circulation. *J Thorac Cardiovasc S.* 1975;69(5):674-84. doi: [https://doi.org/10.1016/S0022-5223\(19\)41499-2](https://doi.org/10.1016/S0022-5223(19)41499-2)
- Brister S, Ofosu F, Buchanan M. Thrombin Generation during Cardiac Surgery: Is Heparin the Ideal Anticoagulant?. *Thrombosis and Haemostasis.* 1993;70(02):259-62. doi: <https://doi.org/10.1055/s-0038-1649561>
- Shore-Lesserson L, Baker R, Ferraris V, Greilich P, Fitzgerald D, Roman P, et al. The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: Clinical Practice Guidelines — Anticoagulation During Cardiopulmonary Bypass. *Ann Thorac Surg.* 2018;105(2):650-62. doi: <https://doi.org/10.1016/j.athoracsur.2017.09.061>
- Young J, Kisker C, Doty D. Adequate Anticoagulation During Cardiopulmonary Bypass Determined by Activated Clotting Time and the Appearance of Fibrin Monomer. *Ann Thorac Surg.* 1978;26(3):231-40. doi: [https://doi.org/10.1016/S0003-4975\(10\)63676-4](https://doi.org/10.1016/S0003-4975(10)63676-4)
- Sniecinski R, Bennett-Guerrero E, Shore-Lesserson L. Anticoagulation Management and Heparin Resistance During Cardiopulmonary Bypass. *Anesthesia & Analgesia.* 2019;129(2):e41-4. doi: <https://doi.org/10.1213/ANE.0000000000003981>
- Choudhury M, Kiran U, Saxena N, Saxena R. Heparin resistance and Marfan syndrome: Is there any correlation?. *J Cardiothorac Vasc Anesth.* 2002;16(1):75-9. doi: <https://doi.org/10.1053/jcan.2002.29687>
- Levy J, Connors J. Heparin Resistance — Clinical Perspectives and Management Strategies. *New Engl J Med.* 2021;385(9):826-32. doi: <https://doi.org/10.1056/NEJMr2104091>
- Durand M, Lecompte T, Hacquard M, Carreaux J. Heparin-induced thrombocytopenia and cardiopulmonary bypass: anticoagulation with unfractionated heparin and the GPIIb/IIIa inhibitor tirofiban and successful use of rFVIIa for post-protamine bleeding due to persistent platelet blockade. *European Journal of Cardio-Thoracic Surgery.* 2008;34(3):687-9. doi: <https://doi.org/10.1016/j.ejcts.2008.05.029>
- Koster A, Loebe M, Mertzlufft F, Kuppe H, Hetzer R. Cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia II and impaired renal function using heparin and the platelet GP IIb/IIIa inhibitor tirofiban as anticoagulant. *The Annals of Thoracic Surgery.* 2000;70(6):2160-2161. doi: [https://doi.org/10.1016/S0003-4975\(00\)01888-9](https://doi.org/10.1016/S0003-4975(00)01888-9)
- Koster A, Kukucka M, Bach F, Meyer O, Fischer T, Mertzlufft F et al. Anticoagulation during Cardiopulmonary Bypass in Patients with Heparin-induced Thrombocytopenia Type II and Renal Impairment Using Heparin and the Platelet Glycoprotein IIb—IIIa Antagonist Tirofiban. *Anesthesiology.* 2001;94(2):245-251. doi: <https://doi.org/10.1097/0000542-200102000-00013>
- Koster A, Chew D, Kuebler W, Habazettl H, Bauer M, Hausmann H et al. Effects of tirofiban on hemostatic activation and inflammatory response during cardiopulmonary bypass. *Am J Cardiol.* 2003;91(3):346-7. doi: [https://doi.org/10.1016/S0002-9149\(02\)03167-3](https://doi.org/10.1016/S0002-9149(02)03167-3)
- Warkentin T, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *The*

- Annals of Thoracic Surgery. 2003;76(6):2121-31. doi: <https://doi.org/10.1016/j.athorac-sur.2003.09.034>
21. Murphy G, Marymont J. Alternative Anti-coagulation Management Strategies for the Patient With Heparin-Induced Thrombocytopenia Undergoing Cardiac Surgery. *J Cardioth Vascula Anesth*. 2007;21(1):113-26. doi: <https://doi.org/10.1053/j.jvca.2006.08.011>
22. Tanaka K, Katori N, Szlam F, Sato N, Kelly A, Levy J. Effects of tirofiban on haemostatic activation in vitro. *British J Anaesth*. 2004;93(2):263-9. doi: <https://doi.org/10.1093/bja/ae1193>
23. Casserly I, Topol E, Jia G, Lange R, Hamm C, Meier B et al. Effect of abciximab versus tirofiban on activated clotting time during percutaneous intervention and its relation to clinical outcomes—observations from the TARGET trial. *The Am J Cardiol*. 2003;92(2):125-9. doi: [https://doi.org/10.1016/S0002-9149\(03\)00525-3](https://doi.org/10.1016/S0002-9149(03)00525-3)
24. Moorehead M, Westengard J, Bull B. Platelet Involvement in the Activated Coagulation Time of Heparinized Blood. *Anesthesia & Analgesia*. 1984;63(4):394-8. doi: <https://doi.org/10.1213/00000539-198404000-00003>