Adverse events and technical complaints related to central venous catheters marketed in Brazil

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Conflict-of-interest disclosure:
The authors declare no competing financial interest

Submitted: 9/12/2012
Accepted: 11/22/2012

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DOI: 10.5581/1516-8484.20130054

***Aim**: The objective of this study was to critically analyze data of the National Notification System for Adverse Events and Technical Complaints (Notivisa) related to central venous catheters, through an evaluation of the description of notifications recorded between 2006 and 2009.*

***Methods**: Notifications were categorized and evaluated to: (i) determine the number of adverse events and technical complaints, (ii) verify compliance with the classification criteria defined by the legislation, (iii) reclassify notifications, when necessary, in order for them to fit in with the legal definitions, (iv) verify registered companies in Brazil, (v) quantify the notifications according to the registered company and product lot, and (vi) identify the country of original of the notified product. Microsoft Excel® 2010 was used to categorize and systematize the data.*

***Results**: Some conceptual errors and incomplete records were found. Altogether, 228 notifications of technical complaints and 119 of adverse events were identified. Some notifications on guidewires and broken catheters were reported which led to the necessity of duplicating some medical procedures and to the occurrence of lesions/lacerations of vessels and tissue injury. Forty-seven percent of companies presented at least one notification in Notivisa and in all, 38 product lots had more than one notification.*

***Conclusion**: These data support a necessity for cooperation between all entities of the National Health Surveillance System to check compliance of this type of product and to properly report adverse events and technical complaints. It is also important to incorporate minimum standards for the management of technologies in health services, including in the acquisition of products and training of staff.*

***Keywords:** Catheter; Central venous catheter; Health Surveillance; National Health Surveillance Agency; Brazil*

Introduction

Central venous catheters (CVC) are classified by the Brazilian health legislation as healthcare products. CVC are very important in the practice of modern medicine, and sometimes essential in the care of hospitalized patients, especially in intensive care units[1-3]. As a rule, individuals who require CVC have health conditions that need greater attention and care and whose clinical condition may be exacerbated by infections or additional interventions performed resulting from problems in the quality of healthcare products[4].

In Brazil, the post-marketing surveillance system of healthcare products is controlled by the National Health Surveillance System (SNVS) but counts on the collaboration of a network of hospitals and other healthcare services (the Sentinel Network), as well as, their own sanitary surveillance institutions[5,6]. One of the instruments available to monitor healthcare products is the National Notification System for Adverse Events and Technical Complaints (Notivisa) created by the National Health Surveillance Agency (ANVISA) in December 2006, through its National Notification and Investigation Surveillance System (NUVIG)[5,6]. Notivisa brings together all notifications of adverse events and technical complaints reported by hospitals of the Sentinel Network, registered companies, other health services and health professionals and also by citizens[5]. Such notifications should be the basis of decision-making aimed at preventing, or at least, minimizing danger, as healthcare products may pose risks that often only become known when the product is available on the market on a large scale.

Hence, the aim of this work was to critically analyze data related to CVC from Notivisa by a detailed assessment of the description of the technical complaints and adverse events reported between 2006 and 2009.

Methods

All reports of adverse events and technical complaints relating to CVC registered with Notivisa between December 2006 and December 2009 were requested from the post-marketing surveillance unit for healthcare products of ANVISA (NUVIG/UTVIG/ANVISA). Data was provided on a Microsoft Excel® 2010 spreadsheet. Upon receipt, the records of notifications were categorized and evaluated in order to: (i) determine of the total number of

adverse events and technical complaints registered in Notivisa, (ii) verify their conformity with criteria stipulated in the manual of the post-marketing surveillance system of ANVISA[5] and Resolution RDC No. 67 of December 22, 2009 of ANVISA[6], (iii) reclassify, when necessary, notifications for them to fit in to the legislation, (iv) check all companies with registrations of this type of product in Brazil, (v) quantify notifications of adverse events and technical complaints according to the registered company and product lot, and (vi) identify the country where the notified products were manufactured. Microsoft Excel® 2010 was used to categorize and systematize the data.

To preserve the identity, each registered company was allocated an alpha-numeric code formed by the letter 'C' followed by a number. Product lots that had more than one notification were also encoded by the letter 'L' followed by a number.

Results

Between December 2006 and December 2009, 347 notifications related to CVC were registered with Notivisa. In December 2006, there was only one notification (0.3%) even though it was found that 15 cases of adverse events and technical complaints registered in 2007 had actually occurred in 2006. Totals of 166 (47.8%), 93 (26.8%) and 87 (25.1%) notifications were registered in 2007, 2008 and 2009, respectively, with six registered in 2008 having had occurred in 2007 and five recorded in 2009 having had occurred in 2008. Among the 87 notifications in 2009, about 70% (n = 59) did not report the date of occurrence and, in some cases, there was an interval of months between the occurrence of the event and its registration in Notivisa.

Of the 347 notifications relating to CVC, different types of adverse events and technical complaints were found each year. It is important to note that for Notivisa, it is the responsibility of the notifier to categorize occurrences as adverse events or technical complaints. Thus, according to the notifiers, 313 technical complaints and 34 adverse events occurred in the study period. However, after a critical and thorough assessment of the description of notifications involving CVC, some cases had been mistakenly identified, i.e. not in accordance with the definitions of technical complaints and adverse events laid out in Resolution RDC 67 of December 21, 2009[5,6]. Using this new classification, 119 adverse events (Table 1) and 228 technical complaints (Table 2) were identified.

The most serious adverse event (Table 1) occurred in 2007, when there was suspicion that the excessive rigidity of a guidewire caused dissection of the aortic ostium leading to the death of a patient. There were large numbers of notifications for some types of adverse events. These included 'the catheter breaking in the patient' (12.0% of notifications) and events related to 'the catheter breaking inside the vessel' with a surgery needed for its removal (5.3%). 'Repetition of the procedure', leading to multiple punctures, which can cause different types of lesions to patients, such as bruising, edema, pain and tissue injury, represented 10.5% of all notifications and 'lesion/laceration of the vessel' caused by deformation of the guidewire during its advance was reported in 8.3% of the notifications. 'Tissue laceration/injury' represented 7.5% of all notifications. In 36.8% of the notifications, although the notifier reported a malfunction of the catheter had occurred during some type of procedure, thus assuming that it occurred during use in a patient, the notifier did not describe the type of damage caused; in the absence of any description, these notifications were classified as 'others'. Notifications of other types

Table 1 - Distribution of adverse events registered in Notivisa between 2006 and 2009 according to the definition in the legislation[5,6]

Description of adverse event	Number of notifications					%
	2006	2007	2008	2009	Total	
Catheter broke in the patient	0	6	4	6	16	12.0
Repetition of the procedure	0	9	2	3	14	10.5
Lesion / laceration of the vessel	0	6	5	0	11	8.3
Tissue laceration / injury	0	2	4	4	10	7.5
Catheter broke inside the vessel leading to a surgical intervention	0	6	1	0	7	5.3
Contamination / infection	0	2	2	1	5	3.8
Variation / increase in arterial pressure	0	0	2	1	3	2.2
Larger incision than necessary	0	1	0	2	3	2.2
Pain	0	2	0	1	3	2.2
Bruising	0	1	2	0	3	2.2
Edema	0	1	1	0	2	1.5
Phlebitis	0	0	0	2	2	1.5
Transitory cerebral ischemia	0	1	0	0	1	0.8
Ventriculitis	0	1	0	0	1	0.8
Death	0	1	0	0	1	0.8
Facility to form blood clots	0	0	1	0	1	0.8
Gaseous embolism	0	0	1	0	1	0.8
Others	0	29	7	13	49	36.8
Total	0	68	32	33	133*	100.0

* The total number of adverse events reported (133) is greater than the total number of occurrences of adverse events (119), because there was more than one type of adverse event for a patient in a single notification.

of adverse events were less frequent however, the seriousness of some of these events is worth highlighting including embolism (0.8%), cerebral ischemia (0.8%) and ventriculitis (0.8%).

Depending on the type of non-compliance reported by the notifier, different levels of harm to health may be envisaged, including temporary or permanent injury to bodily functions or structures, which may or may not be a risk for death, as in the cases described with 'increase/change in blood pressure' (2.2%), 'contamination/infection due to the use of the catheter' (3.8%) and 'ease of clot formation' (0.8%). The occurrence of these complications, in addition to requiring medical and surgical interventions, can result in longer hospitalization.

Of the notifications of technical complaints (Table 2), the most common were those related to the guidewire (50.9%) with the highest number of occurrences being difficulty to advance the guidewire, followed by deformation and excessive flexibility. Another very frequent non-conformity was related to the catheter body (19.8%) with fractures accounting for the highest number of notifications, followed by 'others'; a group that included all cases in which the description of non-compliance was not accurate.

In the current study it was found that 34 companies submitted reports of adverse events and/or technical complaints on their products. This represents about 47% of the companies registered with CVC on the national market. Of these companies, 28 (85%) were importers, one (3%) acted both as an importer and a manufacturer and there was no registration information in ANVISA for one (3%).

The registered importers in this study obtained their products from different countries including Germany, Singapore, South Korea, Egypt, the United States, France, Holland, India, Ireland, Israel, Japan, Mexico, Poland, Portugal, Puerto Rico, Dominican Republic and the Czech Republic. Table 3 lists the ten companies with the highest number of notifications on their products.

Of the notifications registered between 2006 and 2009, 38 product lots had more than one notification with a single product lot in 2008 from company C2 (Table 3) presenting 13 technical complaints and one adverse event reported to Notivisa (Figure 1). In 2007, one product lot from company C2 and another from company C13, presented six (four technical complaints and two adverse events) and five (three technical complaints and two adverse events) notifications, respectively.

Table 2 - Distribution of technical complaints registered in Notivisa between 2006 and 2009 according to the definition in the legislation[5,6]

Description of technical complaint	Number of notifications					%
	2006	2007	2008	2009	Total	
Guidewire (difficult introduction or withdrawal, excessive flexibility, fracture, bent, deformation, fragmenting, stiff, manufactured using 'inappropriate' materials and nonconformity of the introduction system)	1	86	42	36	165	50.9
Body of the catheter (fracture, leakage, hole, cracked, obstructed, rupture, others)	0	30	19	15	64	19.8
Deformity of the dilator and sheath	0	6	3	6	15	4.6
Needle (without hole, broken, cracked, others)	0	7	3	5	15	4.6
Absent (sheath, dilator, needle, demarcations, clamps, radiopacity, connection with equipment)	0	4	3	7	14	4.3
Catheter tract (collapsing, dilating)	0	5	7	0	12	3.7
Problems with the fixing system of the catheter	0	5	7	0	12	3.7
Problems with labeling/package	0	7	0	2	9	2.8
Malfunctions (cuff, connector, clamp, lumen)	0	3	3	2	8	2.5
Register (absent, incorrect)	0	2	3	3	8	2.5
Foreign body	0	0	1	1	2	0.6
Total	1	155	91	77	324*	100

* The total number of technical complaints notified (324) is greater than the total number of occurrences of technical complaints (228) because more than one type of non-compliance was reported in a single notification.

Table 3 - Adverse events and technical complaints recorded in Notivisa for the ten companies with the highest number of notifications between 2006 and 2009

Company	Notifications of technical complaints						Notifications of adverse events					
	2006	2007	2008	2009	Total	%	2006	2007	2008	2009	Total	%
C1 Manufacturer	1	22	12	14	**49**	**21.5**	0	10	4	2	**16**	**13.4**
C2 Importer	0	18	25	1	**44**	**19.3**	0	13	2	1	**16**	**13.4**
C3 Importer	0	13	5	5	**23**	**10.1**	0	5	5	4	**14**	**11.8**
C4 Manufacturer/Importer	0	15	4	2	**21**	**9.2**	0	10	1	1	**12**	**10.1**
C5 Importer	0	7	6	2	**15**	**6.6**	0	5	1	0	**6**	**5.0**
C6 Importer	0	7	3	5	**15**	**6.6**	0	1	5	5	**11**	**9.2**
C7 Importer	0	3	1	9	**13**	**5.7**	0	1	0	3	**4**	**3.7**
C8 Importer	0	0	2	7	**9**	**3.9**	0	0	0	2	**2**	**1.7**
C9 Importer	0	1	2	2	**5**	**2.2**	0	0	2	2	**4**	**3.4**
C10 Importer	0	3	0	1	**4**	**1.8**	0	0	0	0	**0**	**0.0**

* The total number of technical complaints notified (324) is greater than the total number of occurrences of technical complaints (228) because more than one type of non-compliance was reported in a single notification.

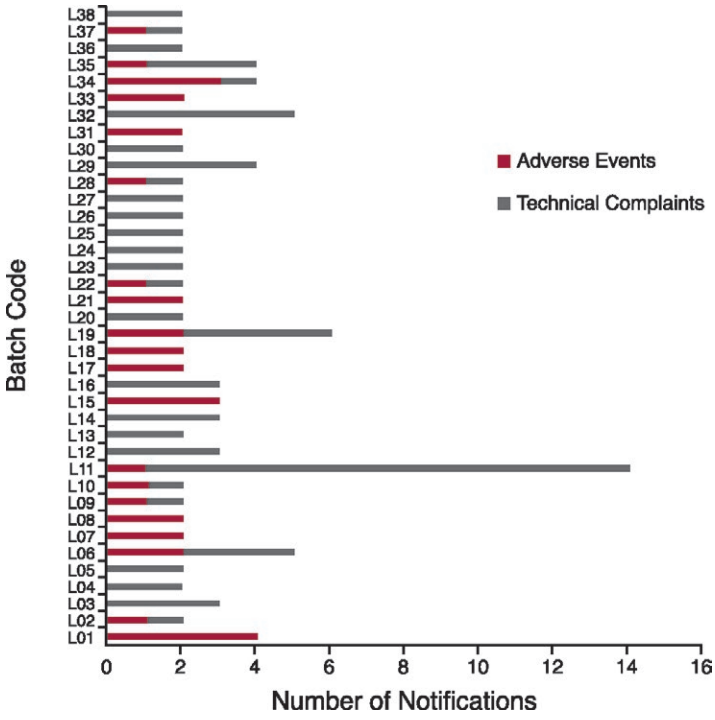

Figure 1 - Technical complaints and adverse event reported to Notivisa

Discussion

A certain degree of risk is intrinsically related to the nature of any product in medicine, so all healthcare products can cause some kind of harm under certain conditions of use.

The safe use of these products must be understood as being a relative term with the occurrence of adverse events being linked to several factors, including: (i) low quality of the product, (ii) its inappropriate use (i.e. errors of procedure), (iii) factors inherent to the patient/user, as well as, (iv) to the degree of risk linked to the specific medical device which is often indicated in its registration in ANVISA[5]. However, according to Brazilian law, when used under adequate conditions and for predefined purposes, healthcare items should act in a way that does not involve excessive harm to human health, and thus it is assumed that the risks inherent to their use are not greater than the expected benefits.

Even though 347 occurrences of adverse events or technical complaints associated with CVC were reported to Notivisa between 2006 and 2009, it is worth mentioning that there is a possibility of under-notification as it is not compulsory for health services to report occurrences and, in the evaluated period, it was still not obligatory for registered companies to report these situations. Moreover, there is also the possibility that for some cases, investigations were opened and concluded by Local, State or Federal Health Departments and thus were not included in the system.

In cases where it was possible to identify the date of occurrence of the event, it was possible to observe that an interval of months passed between the occurrence of the event and its reporting to Notivisa. To ensure that the surveillance measures are carried out properly and timely to prevent a product lot with low quality being used in other patients, it is of the utmost importance that notifications are registered immediately.

Another relevant issue concerns the conformity of notifications with the regulations in force. The identification of the occurrence is made by the notifier; in the present study, there were discrepancies regarding the definitions of technical complaints and adverse events laid down by Resolution RDC 67 of December 21, 2009[5,6].

Based on this finding, a new classification of notifications was made for this study where adverse events are those that cause some type of injury to the patient or user, regardless of the severity, during the use of the product in question under the conditions and parameters stated in the manufacturer's instructions in the registration process at ANVISA; additionally, technical complaints are those involving suspicion of changes/irregularities or low quality of the product before its use in a patient/user[5,6]. Technical complaints, even though they have still not led to an adverse event, may have the potential to cause harm to the individual or collective health.

After a better evaluation according to current regulations[5,6], there was a 250% increase in the number of adverse events (119) compared to the number that had initially been reported to Notivisa. Adverse events incorrectly listed by notifiers as technical complaints included (i) broken needles inside patients, (ii) resistance of the guidewire leading to lacerations of the skin and muscle, and (iii) problems with the needle causing blood vessel injuries.

The most serious adverse event reported was excessive stiffness of the guidewire leading to the death of the patient. It is important to stress that notification of this case, despite its gravity, did not give information about the company, the name of the product, its registration number or the conditions of the patient, data fundamental for the analysis of product-event causality and for the adoption of preventive and corrective measures. An additional 47 notifications of adverse events were incomplete or inappropriate, such as missing information as to the types of injuries caused to patients.

Functional and mechanical failures were reported as technical complaints. Excessive flexibility and stiffness and deformation of the guidewire were the most important functional failures from the point of view of quality and possible harm to the patient. The most serious mechanical failures reported in this study were difficulty in advancing the guidewire and the catheter breaking. All these failures suggest low quality products possibly due to bad catheter design such as the use of inappropriate materials which may lead to irregularities on the surfaces of the devices such as micro-holes and micro-cracks, which can weaken the structure causing cracks and fractures of materials[7].

Today, on considering the set of tests recommended in technical regulations used to evaluate the quality of these products, some of these failures are difficult to check. Thus, the norm NBR ISO 10555-3 - central venous catheters of the Brazilian Association of Technical Standards (ABNT)[8], should have other tests that might identify, even during the manufacturing process, some non-conformance raised in this study, or check the possible causes of nonconformities noted in the post-marketing period. This fact demonstrates the need for the development

of new analytical methodologies to control the quality of these products, such as, scanning using electron microscopy analysis, which would allow a more accurate assessment of the surface and integrity of catheters[9], hence serving as an additional tool to prove that the product meets the specifications claimed by companies at the time of registration. Once developed and regulated, these new methodologies would be compulsorily carried out by manufacturers and used by public health laboratories with the aim of supporting the SNVS to investigate causes of notifications and on the health surveillance measures to be taken.

In this context, it is worth mentioning that all notifications received by Notivisa are read and analyzed, however, investigative and control actions are taken in the light of the seriousness and frequency of adverse events or the potential risk of the notified technical complaint[5]. During the investigation, ANVISA can question the manufacturer/registered company about the notification, which would lead to preventive measures impacting on the quality of the product. In some cases, the action of SNVS may result in the withdrawal of the product lot from the market as was the case of the central venous catheters manufactured by C2, for which, in 2008, importation was suspended, as the product failed to comply with the regulatory requirements of ANVISA. Notifications that are not investigated immediately are held in a database until an analysis of trends demonstrates their importance or an increase in number, thus triggering the opening of an investigation.

The proposal of an international monitoring system for healthcare products is similar to that of Brazil, i.e. risk management to reduce the probability of adverse events and technical complaints, thereby maximizing the safety and efficacy of products.

Conclusion

The evaluation of notifications in Notivisa between December 2006 and December 2009 strongly indicates an increased national risk associated to the use of CVC. Thus, the responsibility of manufacturers and importers is extremely important, mainly with regards to compliance to the requirements established by Resolution RDC No. 59 of June 27, 2000 for the good manufacturing practice of medicinal products and by Resolution RDC No. 56 of April 6, 2011 for the "essential requirements for safety and efficacy of healthcare products" in order to ensure the quality of products and offer the lowest possible risk to the user.

On the other hand, tests prescribed by the regulations in force are insufficient to detect some of the failures observed in the notifications analyzed in this study. Hence, the development of new analytical methodologies followed by updating the rules and the training of public health laboratories may be strong measures to support the actions of technical surveillance.

Consequently, the development of monitoring programs as agreed upon between SNVS institutions should also be considered, in order to verify the quality of healthcare products at the national level by using laboratory tests.

The data from this study also demonstrates the need to incorporate minimum standards for the management of technologies in health services, starting with the process of acquisition up to the disposal of products, including the training of staff members that handle products due to the possibility of errors and of the risk inherent in their use.

Some conceptual differences and incomplete records detected in this study indicate the need for life-long training for the professionals responsible for and involved in the notification process. In this way, some measures are strategic to enhance technical surveillance of healthcare products and prevent or at least minimize harm to the health of the population exposed to this type of products including to increase awareness about Notivisa, discuss with notifiers about the quality and completeness of notifications and divulge examples of failures experienced while interpreting data in this system.

It is important to note that, by registering appropriate notifications, healthcare professionals become essential players in the success of the technical surveillance process and make well-timed health surveillance measures possible. One cannot forget that the greatest importance in the notification process lies in the fact that patterns of failures of both technical complaints and adverse events can be recognized in order to draw up control programs and preventive policies. Prevention of the occurrence of these events should be seen as a priority of everybody involved in this process, from product development to its use. It is also necessary to establish a clear policy to strengthen public healthcare laboratories so that they can play their role in monitoring the quality of healthcare products in the domestic market.

The findings of this study may contribute to a reduction in the risk associated with the use of CVC and the proposed measures will probably be extended to other healthcare products.

Acknowledgements

This work is part of the thesis of Luciene de Oliveira Morais presented in the Master's Course in Public Health of INCQS/FIOCRUZ. Isabella Fernandes Delgado receives a research study grant from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (DT-II/CNPq).

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