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ORIGINAL RESEARCH ARTICLE

Effect of An Educational Intervention to Improve Adverse Drug Reaction Reporting in Physicians: A Cluster Randomized Controlled Trial

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Abstract

Background The yellow-card scheme continues to be one of the principal methods for signal generation in pharmacovigilance. Nevertheless, under-reporting, one of its disadvantages, delays alert signals and has a negative influence on public health. Educational interventions in pharmacovigilance may have a positive impact on the spontaneous reporting of adverse drug reactions (ADRs).

Objectives To assess the duration of the effect and effectiveness of an educational intervention in pharmacovigilance designed to improve ADR reporting in a robust pharmacovigilance system.

Methods A spatial, cluster randomized controlled trial was conducted covering all National Health System physicians in the northwest of Spain and targeting those who were actively engaged in clinical practice ($n = 7{,}498$). Of these, 2,120 were assigned in three spatial clusters to the intervention group (six hospitals and 138 primary care centers) and 3,614 in four clusters to the control group (seven hospitals and 267 primary care centers). The educational intervention consisted of two complementary approaches—one active (group sessions), the other passive (educational material, reporting form)—implemented from November 2007 to December 2008, with a follow-up period of 8 months.

Results Intervention participation was 53.7 % in a hospital setting and 60.5 % in primary care settings. ADR reporting in the intervention group increased by 65.4 % (95 % confidence interval [CI]: 8.2–153.4) across the follow-up. The ADR reporting rate per 1,000 physicians/year in the intervention group rose from 28.1 to 39.6 following the intervention (51.7 and 27.4 in the first and second 4-month period, respectively). For the intervention group, relative risk (RR) was 2.31 (95 % CI: 1.46–3.68) and 1.04 (95 % CI: 0.61–1.77) in the first and second 4-month period, respectively adjusted to baseline values. There was an increase in unexpected ADR reporting (RR 2.06, 95 % CI 1.19–3.55).

Conclusions Pharmacovigilance educational interventions that have proved effective can be successfully applied in different geographical areas. A high baseline notification rate could account for the educational program having a moderate effect.

Key points

The effect of an educational intervention to improve the reporting of adverse drug reactions could depend on the baseline reporting rate in that particular geographical area.

A cluster randomized controlled design is the most appropriate for the minimization of potential sources of bias.

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1 Background

The observation and subsequent reporting of suspected adverse drug reactions (ADRs) in clinical settings remains the groundwork for continuous assessment of the benefit-harm balance of marketed drugs [1]. Under-reporting, which is estimated at 94 % [2], delays alert signals and has a negative influence in public health.

Various health professionals are involved in spontaneous ADR reporting and, in some regions, direct spontaneous ADR reporting by patients is permitted [3, 4]. Nevertheless, physicians continue to be an important pillar of spontaneous reporting of ADRs worldwide and are therefore the main target of educational programs in pharmacovigilance.

In general, educational programs in pharmacovigilance have been said to have a positive impact on both ADR reporting and the relevance of such reporting; and this, moreover, is despite the low level of evidence of the design of the majority of published studies [5]. In addition, high-level evidence studies that have shown a high impact [6, 7] have been undertaken in regions with baseline reporting rates lower than those recommended by the World Health Organization [8, 9].

Accordingly, the aim of this study was to assess the effect and the duration of the effect of an educational intervention in pharmacovigilance designed to improve the quantity and relevance of physician-led spontaneous ADR reporting in a setting with an already high reporting rate [9].

2 Methods

2.1 Study Population and Settings

The study was conducted in Galicia, an autonomous region (*Comunidad Autónoma*) in the northwest of Spain. The local public health system provides hospitalized care at 13 general hospitals (seven referral and six small) and primary care at 405 healthcare centers distributed throughout the territory. The study population consisted of all physicians who were actively engaged in clinical practice in the Galician public health system.

2.2 Study Design

A cluster randomized controlled study was conducted. The two main advantages of this type of design are: first, that potential cross-contamination bias among individuals in the control and intervention groups is controlled for because group allocation is based on spatial clusters rather than individuals; and second, that randomized allocation eliminates potential selection bias. For cluster-formation purposes, particularities of the public healthcare system were taken into account, with each cluster being made up of a referral hospital, small hospitals, and primary healthcare centers in the respective health catchment areas. In view of the geographical, social, and economic differences between Galicia's coastal and inland areas, randomization was stratified by this criterion.

Whereas the intervention group consisted of three clusters, with six hospitals (three referral and three small) and 138 primary healthcare centers, the control group consisted of four clusters, with seven hospitals (four referral and three small) and 267 primary healthcare centers. To increase the efficiency of the intervention, hospital departments were classified by probability of ADR observation. A list of the hospital departments in which the intervention was implemented is shown as electronic supplementary material I.

2.3 Intervention

The educational intervention program combined two complementary approaches, an active component (group sessions) and a passive component (educational material). The presentation, which was dynamic, objective, and brief, was based on an earlier one delivered in north Portugal [6]. The educational session was focused: first, on the importance of reporting ADRs, expressed in terms of morbidity, mortality, and cost; and second, on the limitations of clinical trials for the detection of adverse reactions and the advantages of a spontaneous voluntary reporting scheme. Under-reporting was highlighted as being one of the main disadvantages of this scheme. Moreover, our messages were reinforced to modify attitudes of complacency, insecurity, lack of self-confidence (diffidence), indifference, and ignorance [10, 11], with additional stress being laid on the fact that only a few minutes were needed to complete a yellow-card reporting form. Last, the procedures for reporting to the Galician Pharmacovigilance Center were explained. The presentation took approximately 20–25 min. At the end of the educational session, a specimen yellow card was handed out to each of those attending. The didactic material that was used in the intervention is provided as electronic supplementary material II.

The educational interventions were undertaken by four pharmacy researchers trained in pharmacovigilance. To ensure that the sessions would be as uniform as possible, all researchers met beforehand to agree on the use of common criteria.

2.4 Control Group

Physicians allocated to the control clusters did not attend the scheduled educational intervention but, like their colleagues in the intervention clusters, received the continuing education course imparted by the Galician pharmacovigilance center.

2.5 Follow-Up and Outcome Measurement

The programmed intervention was held from November 2007 to December 2008. The follow-up period began at the end of each cluster intervention and lasted for 8 months. For analysis purposes, follow-up was divided into two 4-month periods. Monthly physician ADR reporting data were anonymously assessed, i.e., without legally protected information, such as that relating to the reporter and patient. The total number of reports, and reports classified as serious, unexpected, and high causality were taken as quantity and reporting relevance indicators.

To ensure data confidentiality, researchers were not given direct access to the original reports. ADR reports were assessed at the Galician Pharmacovigilance Center. To eliminate subjectivity, assessors were kept ignorant of which geographical areas pertained to the control and intervention clusters.

2.6 Statistical Analysis

The statistical analyses were performed on an intention-to-treat basis [12]. This meant that subjects were assigned to the intervention group, and those who failed to attend were also included in the analysis as belonging to the intervention group; the reason for including all subjects in the statistical analysis was to eliminate any selection bias caused by physician non-attendance.

Generalized linear mixed models, using maximum log-likelihood approximated by adaptive Gauss-Hermite quadrature, were applied to the statistical analysis [13]. To construct the models, we used the number of ADR reports as the dependent variable, with individual observations (per month and physician) as level 1, physicians as level 2, and spatial clusters (as indicator variable) as level 3; random effects were considered, both among physicians and among spatial clusters. Because the Poisson assumption (i.e., that the mean and variance of the dependent variable are equal) was not met in our data, the models were fitted with negative binomial response to obtain standard errors corrected for the over dispersion parameter.

To measure the intervention effect, a dichotomous indicator variable was created. This variable (denoted period) takes a value of 0 for the baseline period and 1 for months between the start of the intervention and the end of the follow-up. The intervention effect was assessed by the interaction between the group (1 for intervention group, 0 for control group) and period variables. For analysis of the duration of the effect, another indicator variable was constructed with three categories (0 for the baseline period, 1 for the first 4-month period, and 2 for the second 4-month period after the intervention). The intervention effect in each 4-month period was evaluated by reference to the interaction between this indicator variable and the group variable. Results were expressed as relative risks (RRs) and their 95 % confidence intervals (CIs), indicating the number of times whereby exposure increased the probability of reporting in the intervention vs the control group, adjusted for baseline values.

The results of the generalized linear mixed models were validated by comparing them against results from comparable models obtained by running conditional logistic regression models. All analyses were performed using Stata software [14] (version 13.1).

2.7 Study Registration and Ethical Issues

Approval for the study was obtained from both the Galician Clinical Research Ethics Committee and from hospital management boards and education committees in the intervention group. The study was allocated registry identification number ISRCTN91140684.

3 Results

Overall, participation in the educational intervention in all three clusters was 57.2 %, with participation in primary healthcare and hospital settings being similar at 60.5 and 53.7 %, respectively.

In the pre-intervention period, ADR reporting rates (per 1,000 physicians/year) for all ADR categories studied [total, serious, unexpected, high-causality (defined and probable)] were higher in the control group than in the intervention group, though the difference was not statistically significant. Total ADR reporting in the post-intervention period decreased in the control group and increased in the intervention group (Table 1; Fig. 1), going from 31.3 to 31.1 and from 28.1 to 39.6, respectively.

The effect of the intervention calculated as RR is shown in Table 2. The intervention effect was assessed through the interaction of the group and period variables. The educational intervention increased ADR reporting by 65.4 % (95 % CI 8.2–153.4). Moreover, the educational intervention had a positive effect on the relevance of reporting, measured as the increase in unexpected reports (2.06, 95 % CI 1.19–3.55).

Table 1 Adverse drug reaction reporting rate per 1,000 physicians/year: description by ADR type and period, with the number of reported ADRs shown in brackets

Reporting	Group	Period			
		Baseline	Post-intervention		
			Overall period	4-month period	
				First	Second
Overall	Intervention	28.1 (221)	39.6 (98)	51.7 (64)	27.4 (34)
	Control	31.3 (249)	31.1 (78)	33.5 (42)	28.7 (36)
Serious	Intervention	8.6 (68)	15.7 (39)	20.2 (25)	11.3 (14)
	Control	10.8 (86)	13.2 (33)	12.0 (15)	14.4 (18)
Unexpected	Intervention	5.5 (43)	11.3 (28)	17.0 (21)	5.7 (7)
	Control	5.5 (44)	6.0 (15)	7.2 (9)	4.9 (6)
High causality	Intervention	16.6 (131)	21.0 (52)	28.3 (35)	13.7 (17)
	Control	20.6 (164)	19.1 (48)	19.1 (24)	19.1 (24)

ADR adverse drug reaction, *CI* confidence interval, *RR* relative risk

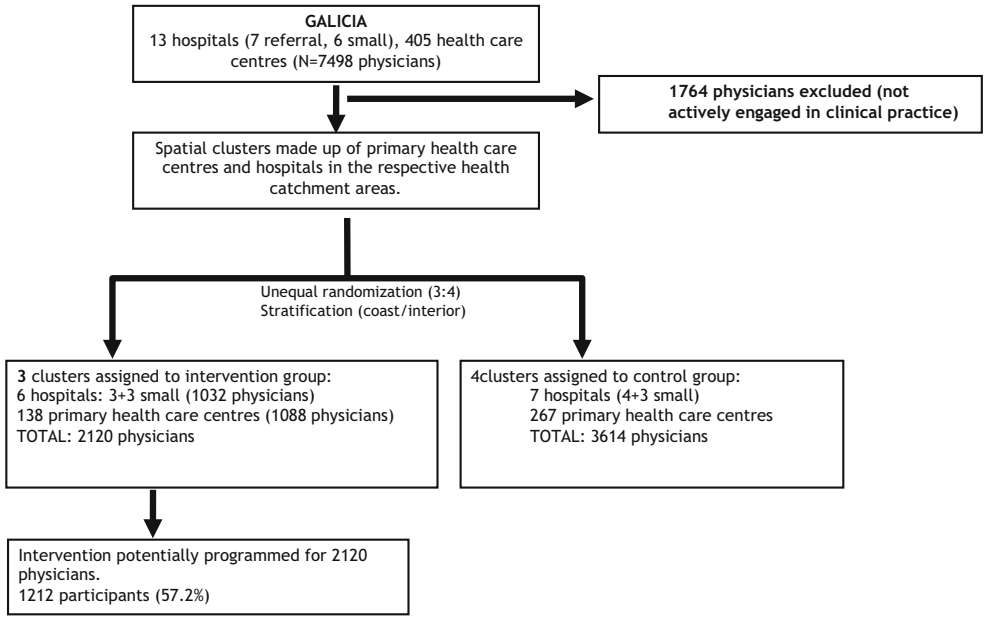

Fig. 1 Study flow chart

The interaction between group and period variables was used to evaluate the duration of the effect of the educational intervention. In the case of total ADR reporting, the effect was greater in the first 4-month post-intervention period (RR 2.31, 95 % CI 1.46–3.68), with the effect's relevance decreasing in the second 4-month period, although it is not statistically significant in comparison with the pre-intervention period (RR 1.04, 95 % CI 0.61–1.77). Similarly, the increase in unexpected ADR reporting remained in evidence in the first 4-month period (RR 3.13, 95 % CI 1.73–5.65, and RR 1.01, 95 % CI 0.43–2.36, respectively) (Table 3).

Applying conditional logistic regression models to these analyses confirmed our results and showed that they are more conservative (see electronic supplementary material III).

4 Discussion

The results of this cluster randomized study indicate that the educational intervention increased ADR reporting by 65.4 % in the 8 months following the intervention. This effect peaked in the first 4-month period and declined in the

Table 2 Relative risk of reporting total, serious, unexpected, and high-causality adverse drug reactions

Independent variables	RR (95 % CI)[a]	*p* value
Effect of intervention on total of ADR reports[b]		
Period	0.89 (0.66–1.22)	0.476
Group	0.89 (0.60–1.32)	0.568
Intervention	1.65 (1.08–2.53)	0.021
Effect of intervention on reports of serious ADRs[b]		
Period	1.06 (0.66–1.70)	0.812
Group	0.65 (0.41–1.02)	0.060
Intervention	1.62 (0.99–2.65)	0.056
Effect of intervention on reports of unexpected ADRs[b]		
Period	1.06 (0.59–1.93)	0.841
Group	0.97 (0.59–1.60)	0.909
Intervention	2.06 (1.19–3.55)	0.010
Effect of intervention on reports of high-causality (defined and probable) ADRs[b]		
Period	0.80 (0.54–1.19)	0.266
Group	0.67 (0.45–0.99)	0.043
Intervention	1.13 (0.72–1.77)	0.603

ADR adverse drug reaction, *CI* confidence interval, *RR* relative risk

[a] RR for period is the adjusted RR of ADR reporting between the pre- and post-intervention period in the control group. It assesses secular trends and possible contamination of the control group by the intervention group. RR for the group category is the adjusted RR of baseline ADR reporting between the intervention group and the control group. RR for intervention measures the adjusted RR of ADR reporting for the intervention itself, as an interaction between the group variable and the period variable

[b] The intracluster autocorrelation is less than 1×10^{-9}

next, while the second is not statistically significant. Not only did the intervention increase ADR reporting overall, it also increased unexpected ADR reporting.

4.1 Comparison between our Study and Others Aimed at Improving Physician Performance

Increases of over 20 % are considered moderately important when assessing the effect of interventions designed to improve health professional practice [15]. In our study, reporting increased by 65.4 % after the intervention. This figure is greater than that achieved by studies that evaluate the effect of interventions to improve physician performance but smaller than the results obtained by other interventions to increase physician ADR reporting [5].

4.2 Comparison between our Study and Others Aimed at Improving ADR Reporting

It is difficult to compare our study to other published interventions to improve physician ADR reporting [16–20], because of variability in design and a lack of published data for calculating the overall effect achieved. Among the reported interventions having a robust epidemiological design and a major educational component, there was one educational intervention, based on a distance-learning program linked to educational credits, which also improved the quantity and relevance of spontaneous ADR reporting [21]. Another intervention, based on educational presentations and monthly reminders, resulted in an increase in spontaneous ADR reporting in hospital settings [22]. Educational sessions plus regular visits by a research assistant increased both the number of ADRs recorded and the number of reporters [23].

The effect achieved by our educational intervention was similar to that obtained by other controlled studies that included physicians in the intervention group [21, 22, 24]. Even so, the relative effect in our study area was less than that achieved in north Portugal, where a similar educational intervention was implemented (RR = 1.65 vs 10.23) [6]. The different baseline reporting rates owing to health professionals in the two study areas prior to the educational intervention, 36 reports per million inhabitants in north Portugal in 2003, and 350 reports per million inhabitants in Galicia in 2006 [25], might have influenced the magnitude of the effect. In fact, the effect of baseline reporting rates about the increase in notifications was also observed in our study, so that in the clusters with smaller initial reporting rates was found a greater effect of the intervention (data not shown). The WHO Monitoring Center in Uppsala considers that reporting rates of over 200 reports per million inhabitants per year are a sign of a mature pharmacovigilance scheme in a country [9]. The reporting rate per million inhabitants per year in Spain for the period 2000–2005

Table 3 Relative risk of reporting total, serious, unexpected, and high-causality adverse drug reactions

Independent variables	RR (95 % CI)[a]	*p* value
Effect of intervention on total no. of ADR reports[b]		
Four-month intervals		
First	1.03 (0.70–1.53)	0.879
Second	0.76 (0.49–1.17)	0.208
Group	0.76 (0.49–1.17)	0.212
Intervention in 4-month intervals		
First	2.31 (1.46–3.68)	<0.001
Second	1.04 (0.61–1.77)	0.883
Effect of intervention on reports of serious ADRs[b]		
Four-month intervals		
First	1.14 (0.62–2.11)	0.672
Second	0.98 (0.52–1.85)	0.949
Group	0.64 (0.41–1.02)	0.058
Intervention in 4-month intervals		
First	2.29 (1.31–4.02)	0.004
Second	1.00 (0.50–2.01)	0.999
Effect of intervention on reports of unexpected ADRs[b]		
Four-month intervals		
First	1.27 (0.61–2.65)	0.520
Second	0.85 (0.36–2.03)	0.720
Group	0.97 (0.59–1.60)	0.903
Intervention in 4-month intervals		
First	3.13 (1.73–5.65)	<0.001
Second	1.01 (0.43–2.36)	0.988
Effect of intervention on reports of high-causality (defined and probable) ADRs[b]		
Four-month intervals		
First	0.88 (0.53–1.46)	0.621
Second	0.72 (0.42–1.24)	0.239
Group	0.67 (0.45–0.99)	0.044
Intervention in 4-month intervals		
First	1.58 (0.95–2.63)	0.076
Second	0.70 (0.37–1.31)	0.258

ADR adverse drug reaction, *CI* confidence interval, *RR* relative risk

*RR for the two 4-month intervals is the adjusted RR of ADR reporting between the pre-intervention period and the two 4-month intervals of the post-intervention period in the control group. It assesses secular trends and possible contamination of the control group by the intervention group. RR for the group category is the adjusted RR of baseline ADR reporting between the intervention group and the control group. RR for intervention measures the adjusted RR of ADR reporting for the intervention itself, as an interaction between the group variable and the two 4-month interval variables

[b] The intracluster autocorrelation is less than 1×10^{-9}

ranks among the 15 highest rates of countries participating in the WHO International Pharmacovigilance Programme [8]. It might be thought that a smaller increase in reporting rates than those observed in studies of similar methodology undertaken in different territories may have been caused by different baseline ADR reporting rates. This might in turn lead one to consider the possibility of a "top" notification rate, which would be difficult to reach in a case where reporting rates were already high.

4.3 Effect Duration

The intervention had a positive extended effect throughout the follow-up on the relevance of ADR reporting, measured as an increase in high-causality reports. The follow-up period was short if compared to those used in other published educational interventions in pharmacovigilance [21–23]. Owing to the termination of the collaboration agreement between the two bodies involved (the university and

the regional authority), the follow-up period could not be extended. In other studies, the effect of interventions has been observed to diminish with time[6].

4.4 Study Strengths and Limitations

This intervention's cluster randomized controlled design is believed to be the most appropriate for the minimization of potential sources of bias, in that: (a) "cluster" minimizes groups' cross-contamination risk; (b) "randomized" minimizes participant selection bias; and (c) "controlled" minimizes the influence of external factors to the intervention on both groups.

Our study is not free of limitations that might modify its effect. First, there was no analysis of the study population's baseline characteristics, including age, sex, medical specialization, work setting (hospital vs primary healthcare), or others of interest, such as years since graduation and continuing specialized education courses. Compilation of all these data was not possible because of confidentiality issues. Similarly, we were unaware of baseline characteristics in the control and intervention groups, and also whether or not these were balanced. Nevertheless, in the event that such differences might have existed, the statistical models used in this study compared pre- and post-intervention variations in ADR reporting for each group, which would have served to eliminate the influence of any confounding factors that remained constant in the pre- and post-intervention periods.

Second, the sessions focused on the attitudes found to be most closely related to under-reporting by previous studies conducted in the same geographical area [11] and in north Portugal [10]. Although we were unable to study the knowledge and attitudes to spontaneous ADR reporting that prevailed immediately prior to the intervention, there is always the possibility that differences vis-à-vis previous studies might have been found. Indeed, a bibliographic review shows consistency in attitudes and knowledge associated with under-reporting in different settings and time periods [26].

Third, participation in the study, rather than being complete, was 57.2 %. The effect could have been greater with total participation. Moreover, health professionals are more likely to participate voluntarily in educational activities pertaining to their subject of interest and, by extension, to a field in which they are professionally experienced [27]. However, because the statistical analysis was performed on an intention-to-treat basis, any selection bias caused by non-attendance was eliminated.

Fourth, four researchers carried out the educational interventions vs a single researcher in another study [6]. Despite the efforts made to agree on common criteria and standardize the interventions, it is of course possible that researchers might have lent a personal touch to the interventions and that this might have affected the end results.

Fifth, an 8-month follow-up period is inadequate to judge an intervention's long-term effect. A previous study has shown that an intervention's effect is more marked in the first 4 months following it [6].

Sixth, owing to confidentiality issues, researchers were not given direct access to the original reporting data and therefore could not evaluate whether the reporters responsible for the effect were those who attended the intervention, if the number of reporters increases, or if those who were already reporters in the baseline period increased their reporting.

Seventh, the effect achieved in overall and in more relevant reporting following the intervention was different. Statistical models with unexpected and serious ADRs have been adjusted but did not converge.

Finally, the educational intervention was essentially didactic, in that it consisted of a presentation and question-and-answer session. A recent review of the effect of continuing education on professional-practice outcomes concludes that mixed interactive and didactic education interventions are most effective [27]. If time for practising the theoretical knowledge acquired is included in scheduled educational sessions (in the form of role play, case discussion, or workshops [18]), this may increase the effect of the intervention. Moreover, a practice-based method achieved more effectiveness in terms of better documented reports and unlabeled events reporting than a lecture-based method [28].

5 Conclusions and Implications

The study shows that educational interventions in pharmacovigilance that have previously proved to have a positive effect could be successfully applied in other geographical areas. Nonetheless, when such interventions are performed in settings with a high reporting rate (with physicians that are more motivated and have the right attitudes towards reporting), it is possible that the effect achieved might be moderate. These findings could indicate that, in high ADR reporting-rate settings, didactic interventions could have a moderate effect and that a more interactive approach would thus be called for. It might be of interest to develop strategies designed to render these types of interventions more attractive to less motivated health professionals. There could well be room for improvement in this group of professionals.

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