Review Article

Administration of antibiotics subcutaneously: an integrative literature review*

Administração de antibióticos por via subcutânea: uma revisão integrativa da literatura

Administración de antibióticos por vía subcutánea: una revisión integrativa de la literatura

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ABSTRACT

Objective: To characterize scientific articles related to the use of antibiotics by the subcutaneous route in patients with difficult venous access in palliative care, regarding local tolerance and therapeutic efficacy. **Methods:** Integrative literature review conducted in the databases of LILACS, CINAHL, PubMED, EMBASE and the Cochrane Library, using Evidence-Based Practice as a theoretical framework. **Results:** Seventeen articles were selected with ten different antibiotics, with ceftriaxone being the most studied antibiotic. Therapeutic efficacy was observed based on pharmacokinetic and clinical parameters. The local tolerance was associated with greater dilution of antibiotics. With administration of aminoglycosides, serious injuries and tissue necrosis were observed. A low tolerance reinforced the restriction of use only to this class of antibiotics. **Conclusion:** The predictions of therapeutic efficacy and good tolerance suggest a possibility to be considered when there is need of an alternative parenteral route of administration, but caution is advised, since none of the studies evaluated patients in palliative care.

Keywords: Anti-bacterial agents/administration & dosage; Injections, subcutaneous; Treatment outcome; Palliative care

RESUMO

Objetivo: Caracterizar os artigos científicos relacionados ao uso de antibióticos por via subcutânea em pacientes com difícil acesso venoso em cuidados paliativos quanto à tolerância local e eficácia terapêutica. **Métodos:** Revisão integrativa da literatura realizada nas bases de dados LILACS, CINAHL, PUBMED, EMBASE e Biblioteca Cochrane, utilizando-se como referencial teórico a Prática Baseada em Evidências. **Resultados:** 17 artigos foram selecionados com dez antibióticos diferentes, sendo o Ceftriaxona, o antibiótico mais estudado. Constatou-se a eficácia terapêutica com base nos parâmetros farmacocinéticos e clínicos. A tolerância local esteve associada à maior diluição dos antibióticos. Com administração de aminoglicosídeos, observaram-se lesões graves e necrose tecidual. A baixa tolerância reforça a restrição de uso apenas para essa classe de antibióticos. **Conclusão:** As previsões de eficácia terapêutica e a boa tolerância sugerem uma possibilidade a ser considerada quando se deseja uma via de administração parenteral alternativa, porém recomenda-se cautela, visto que nenhum dos estudos avaliou pacientes em cuidados paliativos.

Descritores: Antibacterianos/administração & dosagem; Injeções subcutâneas; Resultado de tratamento; Cuidados paliativos

RESUMEN

Objetivo: Caracterizar los artículos científicos relacionados al uso de antibióticos por vía subcutánea en pacientes con difícil acceso venoso en cuidados paliativos en cuanto a la tolerancia local y eficacia terapéutica. **Métodos:** Revisión integrativa de la literatura realizada en las bases de datos LILACS, CINAHL, PUBMED, EMBASE y Biblioteca Cochrane, utilizándose como referencial teórico la Práctica Basada en Evidencias. **Resultados:** Fueron seleccionados 17 artículos con diez antibióticos diferentes, siendo la Ceftriaxona, el antibiótico más estudiado. Se constato la eficacia terapéutica con base en los parámetros farmacocinéticos y clínicos. La tolerancia local estuvo asociada a la mayor dilución de los antibióticos. Con administración de aminoglicosídeos, se observaron lesiones graves y necrosis tecidual. La baja tolerancia refuerza la restricción de uso apenas para esa clase de antibióticos. **Conclusión:** Las previsiones de eficacia terapéutica y la buena tolerancia sugieren una posibilidad a ser considerada cuando se desea una vía de administración parenteral alternativa, sin embargo se recomienda cautela, puesto que ninguno de los estudios evaluó a pacientes en cuidados paliativos.

Descriptores: Antibacterianos/administración & dosificación; Inyecciones subcutáneas; Resultado del tratamiento; Cuidados paliativos.

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INTRODUCTION

The use of the subcutaneous (SC) route for the infusion of large volumes of fluids has been a known practice for over 100 years, both for use in children and in adults, with reports of successful experiences dating from the nineteenth century. [1-3] However, this technique fell out of favor by 1950, due to reports of fluid overload and circulatory shock occurring after SC infusion of large volumes of solutions without electrolytes, [2,4,5] and the disclosure and notification of disastrous results occurring after infusions provided outside the SC tissue also reached the muscle tissue. Another factor that contributed to the disuse of this technique was the ease of application of intravenous (IV) infusions [5].

By 1980, the use of the SC route for medication administration and infusions returned to clinical practice, with emphasis on technical issues related to limiting volume, medicines, infusion time and nursing care, in addition to a selective description of its advantages, disadvantages, indications, contraindications and limitations. [2,6] Since then, this practice has been studied and used in geriatrics and palliative oncology. [2,7]

Specifically regarding SC antibiotics, some studies [8,9] have investigated the pharmacokinetic and clinical parameters, and have converged on a prediction of therapeutic efficacy of the absorption and maintenance of plasma levels. Despite entering the systemic circulation more slowly, their ultimate availability was not affected, with satisfactory results in the treatment of some infections.

With the growing need for a therapeutic approach by means of alternative routes for antibiotic administration in cancer patients in palliative care (PC), the need to increase knowledge and provide support for nursing clinical practice on this issue was also recognized. Thus, this investigation was conducted with the following guiding question: *"What scientific evidence is available about the administration of antibiotics through the SC route on the local tolerance and therapeutic efficacy in patients with difficult venous access in PC?"* Therefore, the objective of this study was: to characterize the scientific articles related to the use of antibiotics by the SC route in patients with difficult venous access in PC regarding local tolerance and therapeutic efficacy.

METHODS

In this study, we performed an integrative literature review, which is one of the research methods of Evidence-Based Practice. This revision responds to a specific question and utilizes explicit and systematic methods to identify, select and critically evaluate the studies. [10] Thus, this specific review method permits the inclusion of diverse research designs (experimental, quasi-experimental and non-experimental). [11,12]

In this regard, the study followed the methodological steps based on reasoned proposals of Ganong [13] and Whittemore and Knafl: [11] Identification of the problem; searching the literature; extraction of data from the studies; evaluation of the studies; interpretation of the results; synthesis of evidenced knowledge.

A broad search strategy was employed, using the electronic databases of LILACS, CINAHL, EMBASE, PubMED and the COCHRANE Library, using *controlled descriptors* – antibiotics, hypodermoclysis, pharmacokinetics, toxicity and absorption; and, *uncontrolled descriptors* or *keywords* – availability and tolerance, using the PICO strategy. [14]

Studies were selected without limitations for publication year or language. The titles and abstracts were analyzed, taking into account the inclusion criteria (articles regarding the use of antibiotics by the SC route); and exclusion criteria (those in which there was use of antibiotics or other medications via the SC route in animals; studies in children; those addressing antibiotic use by other routes of administration; and those which cited other interventions or treatments with antibiotics or other medications via the SC route).

Search strategies were initiated for all databases, using only the controlled descriptors for the initial review. This was followed by insertion of the uncontrolled descriptors; the last review used only the uncontrolled keywords.

Initially, a pre-selection was made of the articles found in the performed searches by means of reading the title and abstract, and when questions arose regarding the content of the work, these were pre-selected for subsequent complete analysis. In cases in which only the title of the article was available, portraying with clarity that the content of the study did not meet the purpose of the review, it was excluded; but in the cases that generated uncertainty, the study was also included for further analysis. Figure 1 shows a schematic of the sampling of this integrative review.

After completing the search strategies, we proceeded to collect data, using the instrument of Ursi [15], with open- and closed-ended questions, composed of five items: identification, institution in which the study was based, type of scientific journal, methodological characteristics of the study, and evaluation of methodological rigor.

Studies were classified by hierarchical levels of evidence, according to the assumptions of Melnyk and Fineout-Overholt [16]; the assessment of methodological quality of Randomized and Controlled Clinical Trials (RCCT) was conducted using the scale of Jadad et al.[17].

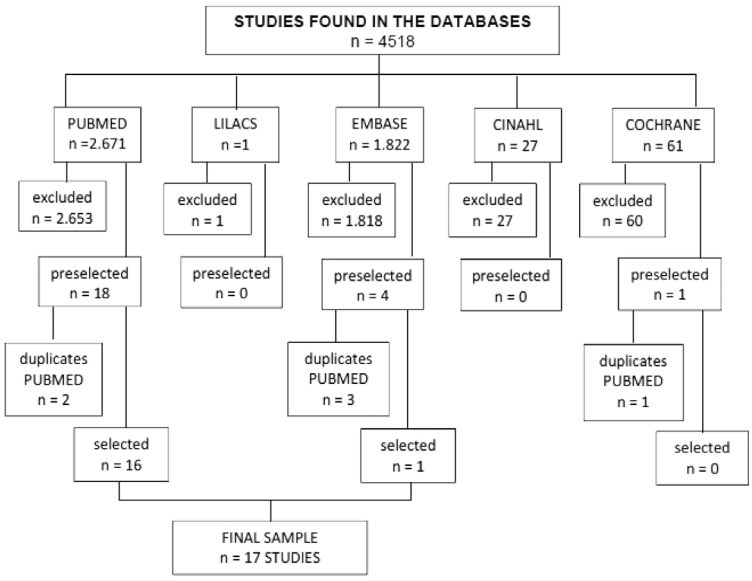

Figure 1. Sampling for the integrative review..

Table 1 – Studies included in this integrative review in relation to the authors, year of publication, title, research design, level of evidence, Jadad score and thematic category. Ribeirão Preto, 2011

Autores Ano	Title	Research design	Level of evidence	Jadad Score	Thematic category
Frasca et al. (2010)[22]	Pharmacokinetics of Ertapenem following intravenous and subcutaneous infusions in patients	Quasi-experimental	III		Therapeutic efficacy; Local Tolerance
Harb et al. (2010)[19]	Safety and pharmacokinetics of subcutaneous Ceftriaxone with or without administered recombinant human hyaluronidase (rHuPH20) versus intravenous Ceftriaxone administration in adult volunteers	RCCT	II	3	Therapeutic efficacy; Local Tolerance
Robelet et al. (2009)[27]	Antibiotiques par voie sous-chez la personne agee cutanée [Antibiotics given subcutaneously in the elderly]	Integrative review	V		Therapeutic efficacy; Local Tolerance
Walker et al. (2005)[9]	Subcutaneous administration of Cefepime	Quasi-experimental	III		Therapeutic efficacy; Local Tolerance
Barbot et al. (2003)[23]	Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous Teicoplanin in critically ill patients without vasopressors	RCCT	II	1	Therapeutic efficacy; Local Tolerance
Melin-Coviaux et al. (2000)[8]	Pharmaco-Étude de la clinique comparative Ceftriaxone par voie sous-cutanée chez la personne et intraveineuse Agee [Pharmaco-clinical comparative study of Ceftriaxone by subcutaneous and intravenous administration in the elderly]	RCCT	II	1	Therapeutic efficacy; Local Tolerance
Champoux et al. (1996)[24]	Single-dose pharmacokinetics of Ampicilin and Tobramycin administered by hypodermoclysis in young and older healthy volunteers	Quasi-experimental	III		Therapeutic efficacy; Local Tolerance
Platin et al. (1993)[25]	Necroses cutanées injections après-sous d'cutanées Amikacine [Skin necrosis after subcutaneous injections of Amikacin]	Experience report	VI		Local Tolerance
Bricaire et al. (1998)[20]	Étude de la pharmacocinétique et de la de la tolérance Ceftriaxone administrée par voie sous-cutanée [Study of the pharmacokinetics and the tolerance of Ceftriaxone administered subcutaneously]	Quasi-experimental	III		Therapeutic efficacy; Local Tolerance
Bernard et al. (1987)[33]	Vasculitis cutanée localisée induite pair Nétilmicine La sous-cutanée [Localized cutaneous vasculitis induced by subcutaneous Netilmicin]	Experience report	VI		Local Tolerance
Duterque et al. (1985)[32]	Lesions nécrotiques pair injections sous-cutanées of Gentamicin et de Sisomicine [Necrotic lesions in subcutaneous injections of Gentamicin and Sisomicin]	Experience report	VI		Local Tolerance
Borner et al. (1985)[21]	Comparative pharmacokinetics of Ceftriaxone after subcutaneous and intravenous administration	RCCT	II	0	Therapeutic efficacy; Local Tolerance
Doutre et al. (1985) [28]	Necroses cutanées après-sous cutanée administration of Gentamicin [Skin necrosis after subcutaneous administration of Gentamicin]	Experience report	VI		Local Tolerance
Tailandier et al. (1984) [30]	Necroses cutanées induites par la Gentamicin-sous cutanée [Skin necrosis induced by subcutaneous Gentamicin]	Experience report	VI		Local Tolerance
Penso et al. (1980)[29]	Necroses cutanées après-sous cutanée administration of Gentamicin [Skin necrosis after subcutaneous administration of Gentamicin]	Experience report	VI		Local Tolerance
Bonnetblanc et al. (1980)[31]	Vasculitis cutanée à la Gentamicin [Cutaneous vasculitis with Gentamicin]	Experience report	VI		Local Tolerance
Leng et al. (1979)[26]	Pharmacocinétique comparée of I'Amikacine après administration intraveineuse, intramusculaire et sous-cutanée [Comparative pharmacokinetics of Amikacin after intravenous, intramuscular and subcutaneous administration]	Quasi-experimental	III		Therapeutic efficacy

RESULTS

Regarding the design of the studies, seven were experience reports, five were quasi-experimental, four were Randomized Controlled Clinical Trials (RCCT), and one was an integrative review. In considering the levels of evidence, [16] four studies were categorized as evidence level II (strong), five studies were evidence level III (moderate), and eight studies were evidence level V and VI (weak). The methodological quality of the four RCCT was assessed, [17] of which the final score of three of them was poor (Jadad 0 and 1) and only one study obtained a moderate final score (Jadad 3), according to the data in Table 1.

The studies were classified into two thematic categories, based on pharmacokinetic aspects that characterized the predictions of therapeutic efficacy and tolerance aspects at the SC insertion site. Thus, the *Therapeutic efficacy* category was present in ten studies, and *Local tolerance* was found in 16; nine of the studies presented both thematic categories. No studies were found that addressed the patient in PC.

After categorization, we identified 10 different antibiotics belonging to five classes; the Aminoglycoside class had the largest number of studies. Of these antibiotics, the most cited was *gentamicin* (in five studies) followed by *amikacin* (in two studies). The second class of antibiotics with a large number of studies was the 3rd generation cephalosporins, with a greater identification with *ceftriaxone* (in four studies), as demonstrated in the data of Table 2.

Table 2 – Presentation of antibiotics according to the class and name of the antibiotics present in the studies.Ribeirão Preto, 2011

Class of antibiotic		Name antibiotic
Cabapenêmicos		Ertapenem [22]
Cephalosporins	3rd generation	Ceftriaxone [8,19,20,21]
	4th generation	Cefepime [9]
Glycopeptides		Teicoplanin [23]
Penicillins		Ampicillin [24]
Aminoglycosides		Tobramycin [24]
		Amikacin [25,26]
		Netilmicin [33]
		Gentamicin [28,29,30,31,32]
		Sisomicin [32]

DISCUSSION

The thematic category of *therapeutic efficacy* was evaluated based on the pharmacokinetic parameters of the antibiotics, of which C_{max} (highest concentration in the bloodstream), T_{max} (time required to reach maximum concentration), AUC (area under the curve), $t_{1/2}$ (time of half-life of elimination), bioavailability and MIC (minimum inhibitory concentration) [18] were considered.

In relation to *ceftriaxone*, [8,19-21] despite the fact that the C_{max} was lower for the SC route than for IV, with initial plasma levels achieved lower for SC than for IV, fully satisfactory plasma levels were achieved, with prolonged time of action and a very similar absorption rate to the intravenous (IV) and intramuscular (IM) routes. The use of *hyaluronidase* [19] increased absorption capacity subcutaneously, increased the C_{max} , and added one hour to the $T_{max.}$ When we compared the SC and IV routes, [8] it was possible to confirm a state of equilibrium for the two routes of administration and 100% of bioavailability for the SC route. The residual rates of the plasma *ceftriaxone* therapeutic indices were much higher than the MIC of the micro-organisms causing infections. Based on these data, it is possible to affirm that a presumption of therapeutic efficacy exists, guided by the pharmacokinetic parameters evaluated. For *cefepime* [9], the comparison of pharmacokinetic parameters for the IM and SC routes was similar, converging on a presumption of therapeutic efficacy for this antibiotic subcutaneously.

Infusion of *ertapenem* [22] subcutaneously was equivalent to the IV route in terms of estimated therapeutic efficacy, and could be an alternative to the IV route, according to the results. However, this study had a small sample (n = 6), which may be insufficient for safely extrapolating the results to other populations.

In the study of *teicoplanin*, [23] the SC route supported the maintenance of therapeutic levels for a longer time than the IV route, and reached greater therapeutic indices than the MIC.

The SC route for *ampicillin* and *tobramycin* [24] slightly modified the pharmacokinetic parameters of both antibiotics. Small changes were observed in the absorption, distribution and elimination, when comparing the SC and IV routes, but these did not advise against use of the SC route. To the contrary, the pharmacokinetic data that converge to prove therapeutic efficacy suggested that there is potential utility of the SC route for antibiotics and other medications.

The administration of *amikacin* [25,26] subcutaneously permitted elevated and early serum levels, and the IM and SC routes were bioequivalent. It is noteworthy that the results about the effectiveness of the medicine based on the pharmacokinetic parameters assessed speak in favor of using the SC route for administration of this antibiotic. However, this study [26] was limited by the absence of inclusion and exclusion criteria, statistical comparisons between the pharmacokinetic parameter values, and the low number of only five participants, which limits extrapolation of the results to other populations.

In the integrative review study, [27] the authors emphasized that, although there were advantages in the

use of this route, studies encountered had a low level of recommendation (level B and C) according to the reference used. Therefore, caution is necessary, especially for the aminoglycoside class.

For the thematic category, *Local tolerance*, injuries, pain, warmth, itching, redness, and swelling after SC antibiotic administration were evaluated. In the seven case reports with *gentamicin* [28-32], *sisomicin* [32] and *netilmicin* [33], the appearance of skin lesions was observed, with the majority of cases evolving to necrosis. Even though the studies pointed to healing or improvement of the characteristics of the lesions, it does not seem advisable to use the SC route for this class of antibiotics (aminoglycosides), without first having confirmation of pharmacological aspects and safety by means of other studies.

Research conducted with the antibiotics *ampicillin* and *tobramycin* [24] confirmed that there was good local tolerance via the SC route in research subjects, suggesting the potential utility of this route of administration for antibiotics, yet presenting caveats that more studies are necessary, in order to define precisely the safe dose.

With respect to *teicoplanin*, [23] there was good tolerance by the SC route in septic patients, and the authors recommended the use of this route for other drugs as well in patients who required long-term treatment or who had no possibility of IV access, including the PC patients.

With *ertapenem*, [22] the results were favorable by the SC route in the study population, strengthening the possibility of the indication of these carbapenems. However, for the results of tolerance to be extrapolated safely, it is necessary to construct other studies evaluating parameters of tolerance in larger and heterogeneous populations.

For *cefepime*, [9] the lower pain scores during and after the infusion, with the final result of high overall acceptability, showed that the subcutaneous infusion was well tolerated, with minimal discomfort. It is emphasized however, that the single dose administration may have favored the high tolerance and acceptability of the SC route, for the administration of *cefepime* in this study.

In relation to the comparison of studies about local tolerance with *ceftriaxone*, the study by Borner et al. [21] was the only one that denied the presence of any reaction of local intolerance at the dose of 0.5 g. Other studies by Harb et al., [19], Melin-Coviaux et al., [8] and Bricaire et al., [20] confirmed the presence of at least one event related to the doses used; in the study by Bricaire et al., [20] in which the dose was 2 g, more serious complications were observed. The usual therapeutic dose for *ceftriaxone* is 1 g, but it was evident that 0.5 g was better tolerated, however this dose did not reach therapeutic indices [21].

Thus, the aminoglycosides presented a poorer local tolerance by the SC route; only with *tobramycin* [24] were no reports made of intolerance. The data presented on cephalosporins was conflicting, according to the dose used; in the study with improved tolerance, a lower dose and *lidocaine* were used simultaneously. In relation to penicillins, the authors concluded that the prescribed dosage was not sufficient to finalize conclusions regarding tolerance.

CONCLUSION

This research has enabled information regarding the therapeutic efficacy and local tolerance of antibiotics by the SC route. However, it is important to emphasize that this study was limited regarding the level of evidence: only four of the 17 studies presented a strong level of evidence, and of these, three had low methodological quality scores.

It was also observed that the lack of antibiotics delivered by the SC route in patients in PC showed the need for research that will strengthen the everyday practice of nursing in the PC, both in home care, in ambulatory care or in hospitalization, whereas the real benefits with the use of the parenteral route are evident.

This is considered to be pioneering work in nursing with this theme that presents existing recommendations on the use of antibiotics through the SC route. It is also important because in general, the performance of the procedure, the care for the insertion of the devices, administering medication, assessing the conditions of vascular access, and monitoring of local reactions in patients are activities performed by these professionals. This work opens the possibility for future research in this area which has been little explored by nurses, but which is absolutely necessary in order to add knowledge to safe and quality practice, thereby strengthening Evidence-Based Practice in Nursing.

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