Hypodermoclysis: a literature review to assist in clinical practice

Hipodermóclise: revisão de literatura para auxiliar a prática clínica

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ABSTRACT

The aim of this study was to analyze the information available in the literature about the drugs that can be administered through hypodermoclysis and the resulting impact that this information may have on the routine of the pharmacist working at a hospital. The study was based on a review of the literature. The results showed positive points of the procedure, but little specific information about medications such as routes of administration, standard dilutions, optimal doses, etc. Thus, it was possible to verify that there is no definite information as to the correct way to administer the drugs in this route, even though this is an effective and safe option, according to the literature. The lack of information has a negative impact on the support provided by the pharmacist to the nursing staff to ensure that the drug actually reaches its therapeutic goals safely.

Keywords: Hypodermoclysis; Palliative care; Infusions, subcutaneous

INTRODUCTION

Hypodermoclysis is also known as the administration of fluids by the subcutaneous route. It is an ancient practice and was first reported in 1913, but because of the adverse events resulting from its inadequate use, such as the use of hypertonic solutions, the practice was abandoned.\(^1(1)\)

It has been used in patients who present with diagnoses of moderate dehydration caused by severe dysphagia, dementia, intestinal obstruction due to neoplasms, and somnolence. There is also the possibility of administering medications to those patients who have no conditions for a peripheral venous access puncture.\(^1(1,2)\)

Hypodermoclysis is also described as a simple practice and less expensive than the other techniques.\(^6)\)

The medications and fluids given by hypodermoclysis are absorbed by means of capillary diffusion mechanisms. Patient edema and hematomas may hinder treatment.\(^11,12)\)

The pharmacokinetics are similar to those of medications administered by intramuscular route, but display a prolonged time of action, besides better tolerability for
those medications with a pH close to neutral and that are hydrosoluble.\textsuperscript{(11)}

In order to facilitate administration of medications by hypodermoclysis, some literature suggests the use of hyaluronidase, as this is an enzyme that decomposes the hyaluronic acid present in the tissue, leading to decreased viscosity and thus increasing the rate of absorption of the drugs given.\textsuperscript{(3)}

There are locations (puncture sites) that are more appropriate for therapy, such as the deltoid region, anterior chest region, scapular region, abdominal regional, and anterior and lateral sides of the thighs. (Figure 1)

For professional prescribers, in general, indication of route of administration is based on the international literature or on one’s own clinical experience, which is not reported in official articles.

For the local Pharmacy, the lack of reliable information generates certain difficulties when evaluating a medical prescription, as well as in instructing the nursing team as to the necessary care for use of the prescribed drug, since each medication has its own exclusive characteristics, such as pH, stability, besides appropriate dilution and diluent volumes.

Since there is little information in literature on this topic, the interest arose to analyze, by means of this study, what national and international literature has become available on hypodermoclysis and to what extent this information may be valuable to the pharmacist, since this professional is the one responsible for the medications within a hospital.

METHODS

This is a bibliographic research, with review of literature. Books and manuals on Palliative Care were consulted, and searches conducted for articles and guidelines in the databases Scientific Electronic Library Online (SciELO), MEDLINE, and Google Scholar. The keywords used were “hypodermolysis”, “Palliative Care”, and “subcutaneous route”, published in Portuguese and English, within a timeframe that included the years 1999 to 2012.

The articles were analyzed according to the objective proposed so that the papers that had information related to the use of medications and the method of their use, hydratrating solutions (0.9% sodium chloride, 0.45% sodium chloride, and 5% glucose), besides the advantages and disadvantages of the technique and possible adverse reactions.

Many of the studies and guidelines found in preparing this study were international. Even so, they do not offer a large amount of information as to the topic, especially as to the use of drugs.

The information was tabulated on an electronic spreadsheet (EXCEL) and presented in the form of charts and tables.

To prepare the chart related to compatibilities, the Micromedex\textsuperscript{®} electronic database was used as a tool.

Chart 1 presents information on the medications cited in the articles.
### Chart 1. Table of medications most often used by subcutaneous route

| Drug               | Indication                      | Doses                      | Most indicated diluent | Infusion time indicated | Comments                                      |
|--------------------|---------------------------------|----------------------------|------------------------|-------------------------|-----------------------------------------------|
| Ampicillin*        | Infections                      | 500mg/day                  | *                      | *                       | *                                             |
| Atropine           | *                               | 1.2mg/once a day           | *                      | *                       | *                                             |
| Cefepime           | Infections                      | 1g/day                     | SS                     | *                       | *                                             |
| Cefotaxime*        | Infections                      | 500mg/day                  | SS                     | 30 minutes              | *                                             |
| Ceftazidime*       | Infections                      | 500mg/day                  | SS                     | 30 minutes              | *                                             |
| Ceftriaxone*       | Infections                      | 1g/day                     | SS                     | 30 minutes              | *                                             |
| Ketorolac          | Intense pain                    | 30-90mg/day                | SS                     | *                       | Exclusive route                                |
| Cyclizine          | Nausea and vomiting             | 25-50mg every 8 hours (maximum of 150mg/day) | Continuous inf. = DW | *                       | Incompatible with SS                          |
| Clonazepam         | Agitation and anxiety           | 5-8mg/day                  | SS or DW               | *                       | Is an irritant, dilute to maximum tolerated   |
| Dexamethasone      | 1. Increased intracranial pressure  | 1. 4-16mg/day | SS or DW            | *                       | Exclusive route                               |
|                   | 2. Reduction of peritumor edema | 2. 4-40mg/day              |                        |                         |                                                |
|                   | 3. Dyspnea                      | 3. 8-24mg/day              |                        |                         |                                                |
|                   | 4. Nausea and vomiting          | 4. 8-20mg/day              |                        |                         |                                                |
| Diclofenac         | Pain                            | 75-150mg/day               | SS                     | *                       | Is an irritant, dilute to maximum tolerated   |
| Dipyrone           | Pain                            | 1g up to every 6 hours     | SS                     | *                       | Exclusive route                               |
| Scopolamine        | Intestinal cramps               | 60-180mg/day               | DW                     | *                       |                                                |
|                   | Maximum of 40mg/day in           |                           |                        |                         |                                                |
|                   | continuous infusion             |                           |                        |                         |                                                |
| Famotidine         | Gastric protector               | *                         |                        | *                       |                                                |
| Phenobarbital      | Confusion                       | 200mg/day                  | DW                     | *                       | Exclusive route, even though compatible with morphine |
| Fentanyl           | Pain                            | Usual: 100-1,000mcg/day    | SS                     | 1mL/H=5mcg/h            | (solution of 500mcg in 100mL of diluent)      |
| Furosemide         | Dyspnea due to pulmonary        | 20-40mg                    | SS                     | *                       |                                                |
| Granisetron        | Nausea and vomiting             | 3-9mg/day                  | 50mL SS                 | >10 minutes             |                                                |
| Haloperidol        | Nausea and vomiting Sedation, agitation | 2.5-10mg/day             | DW                     | *                       | Maximal concentration of 2mg/mL. SS may precipitate |
| Hydromorphone      | Pain                            | 50% of oral dose           |                        | *                       |                                                |
| Hydroxyzine        | Antiallergic                    | *                         |                        | *                       |                                                |
| Levomepromazine    | Intense nausea and vomiting     | 5-100mg/day                | SS                     | *                       | Is an irritant, dilute to maximum tolerated   |
| Methadone          | Intense pain                    | 50% of oral dose           | SS                     | 60mL/h                  | Is an irritant, vary the puncture site every 24 hours |
| Metoclopramide     | Nausea and vomiting             | 30-120mg/day               | DW                     | *                       | Is an irritant, dilute to the maximum tolerated |
| Midazolam          | 1. Agitation and confusion in terminal patients | 1. 10-60mg/day | SS or DW              | *                       | Is an irritant, dilute to the maximum tolerated |
|                   | 2. Multifocal myoclonus         | 2. 10-30mg/day             |                        |                         |                                                |
|                   | 3. Hiccups                      | 3. 30-120mg/day            |                        |                         |                                                |
|                   | 4. Sedation                     | 4. Initiate with 1mg/h and increase to 4mg/h |                        |                         |                                                |
| Morphine           | Pain and dyspnea                | 50% of oral dose           | SS or DW               | *                       | A dose of 10mg/mL can be given every 4 hours |
| Naproxen           | Pain                            | 550-600mg/day              | *                      | *                       | Incompatible with morphine                    |
| Octreotide         | 1. Reduced gastric secretion, motility, vomiting and diarrhea | 1. 300-600mcg/day (maximum of 1,500mcg) | SS                     | *                       | Is an irritant                                |
|                   | 2. Intestinal obstruction       | 2. 250-500mcg (maximum of 750mcg) | SS                     | *                       |                                                |
|                   | 3. Intractable diarrhea         | 3. 50-500mcg (maximum of 1,500mcg) | SS                     | *                       |                                                |
| Ondansetron        | Nausea and vomiting             | 8-24mg/day                 | SS or DW               | *                       |                                                |
| Promethazine*      | Nausea, Antiallergic            | 12-25mg/day                | *                      | *                       |                                                |
| Ranitidine         | Gastric protector               | 50-150mg/day (maximum of 300mg) | DW                     | *                       |                                                |
| Tobramycin*        | Infections                      | 75mg/day                   | *                      | *                       |                                                |
| Tramadol           | Pain                            | 100-600mg/day              | SS                     | *                       |                                                |

Adapted from: Ferreira KA and Santos AC.*

*Pereira I. Cuidado paliativo. São Paulo: CREMESP; 2008. Hipodermoclise. p. 260-72. DW: distilled water; SS: saline solution; *: no information available.
RESULTS
According to the methodology cited for search of information, 17 pieces of literature (Chart 2) and an electronic database were selected.

The selection of articles resulted in the following findings: five papers covering only information related to the procedure of hydration, i.e., no medications were mentioned, four only focused on the use of medications, and eight presented both types of information. Only five articles cited information related to the form of preparation and administration of the medications.

Of the articles selected, 10 had information related to the advantages and disadvantages of the method, (Chart 3), and only two references did not cite any adverse reactions.[(5,13)]

Most often reported adverse reactions were pain, inflammation at the puncture site, and even edema and tissue necrosis.[(3,6,8,12,14,15)]

In one of the articles located, 57 patients were accompanied at a Prolonged Stay Institution for the Elderly (ILPI, acronym in Portuguese) and received hydration by hypodermoclysis; 88% of them showed improvement of the general clinical status and 84% showed improvement in cognitive status after the use of hypodermoclysis.[(12)]

As to information related to medications, very little has been written since few drugs have been studied to date using this route, and few have license for use in subcutaneous infusions.[(14)] According to one of the articles analyzed, in which an open questionnaire was answered by physicians as to the types of medications most commonly

| Chart 2. Literature selected in databases |
|------------------------------------------|
| **Author** | **Title** | **Year** | **Medications/ hydration/both/not cited** | **Advantages and disadvantages** | **Adverse reactions** | **Mode of preparation and administration of medications** |
|------------|-----------|---------|----------------------------------|--------------------------------|-----------------|----------------------------------|
| Pereira I[(5)] | Cuidado Paliativo. Conselho Regional de Medicina do Estado de São Paulo - CREMESP Hipodermóclise | 2008 | Both | Yes | Yes | No |
| Jain S et al.[(2)] | Subcutaneous fluid administration – better than the intravenous approach? | 1999 | Both | Yes | Yes | No |
| Conselho Regional de Enfermagem de São Paulo[(2)] | Hipodermóclise | 2009 | Both | Yes | Yes | No |
| Takaki CY et al.[(4)] | Hipodermóclise: o conhecimento do enfermeiro em unidade de internação | 2010 | Both | Yes | Yes | No |
| Marques C et al.[(5)] | Terapêutica subcutânea em cuidados paliativos | 2005 | Medications | No | No | No |
| Yap LK et al.[(4)] | Hypodermoclysis or subcutaneous infusion revisited | 2001 | Hydration | No | Yes | No |
| Ferreira KA et al.[(4)] | Hypodermoclysis and administration of medications by subcutaneous route. A technique from the past with a future | 2009 | Both | No | Yes | Yes |
| Griffiths A[(8)] | Clinical Guideline for Subcutaneous Infusion (Hypodermoclysis). INHS South Gloucestershire | 2010 | Hydration | Yes | Yes | No |
| Remington R et al.[(4)] | Hypodermoclysis to Treat Dehydration: A Review of the Evidence | 2007 | Hydration | Yes | Yes | No |
| Sasson M et al.[(15)] | Hypodermoclysis: an alternative infusion technique | 2001 | Hydration | Yes | Yes | No |
| Instituto Nacional do Câncer[(17)] | Série Cuidados Paliativos. Terapia Subcutânea no Câncer Avançado | 2009 | Both | Yes | Yes | Yes |
| Arinzon Z, et al.[(12)] | Hypodermoclysis (subcutaneous infusion) - effective mode of treatment of dehydration in long-term care patients | 2004 | Hydration | No | Yes | No |
| Frasca D, et al.[(13)] | Pharmacokinetics of Ertapenem Following Intravenous and Subcutaneous Infusions in Patients | 2010 | Medications | No | No | Yes |
| NHS Greater Glasgow and Clyde[(17)] | Guideline for the Use of Subcutaneous Medications in Palliative Care for Adults | 2010 | Medications | Yes | Yes | No |
| Azevedo EF, et al.[(15)] | Administration of antibiotics subcutaneously: an integrative literature review | 2012 | Medications | No | Yes | No |
| Azevedo EF, et al.[(15)] | Manual de Cuidados Paliativos. Academia Nacional de Cuidados Paliativos – ANCP. Hipodermoclise: um método alternativo para infusao de fluidos e medicacoes pela via subcutanea | 2009 | Both | Yes | Yes | Yes |
| Fonzo-Christe C, et al.[(17)] | Subcutaneous administration of drugs in the elderly: survey of practice and systematic literature review | 2005 | Both | No | Yes | Yes |
Chart 3. Advantages and disadvantages of hypodermoclysis\(^{(1-4,9,11,14,16)}\)

| Advantages                                                                 | Disadvantages                                                                 |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Low cost                                                                  | Usual infusion time of 1mL/minute                                             |
| More comfortable than intravenous administration                         | Only 3,000mL over a period of 24 hours may be infused and should be fractioned at different sites |
| Easier to obtain new administration sites                                 | May lead to local edema                                                      |
| May be done in homecare/hospice                                           | Is limited to the administration of electrolytes                             |
| Reduction of hospitalizations                                             | Nutritional supplements and hypertonic solutions are not indicated           |
| Few reports of thrombophlebitis cases                                     | Possibility of local reactions                                               |
| Has not been related to infections and sepsis                             | Not indicated in cases of severe dehydration                                 |
| Maybe installed and interrupted easily, opening and closing the infusion system | In urgency and emergency cases                                               |
| Has not been associated with clot formation                               | In cases of severe bacterial infections                                       |
| Does not require complex materials                                        |                                                                               |

Chart 4. Compatibility among medications by hypodermoclysis\(^{(16,18)}\)

| Ampicillin | Atropine | Clonazepam | Chlorpromazine | Dexamethasone | Famotidine | Fentanyl | Haloperidol | Hyoscine | Insulin | Ketamine | Methadone | Metoclopramide | Midazolam | Morphine | Octreotide | Ondansetron | Ranitidine | Tramadol |
|------------|----------|------------|----------------|---------------|------------|----------|------------|----------|---------|----------|-----------|----------------|-----------|----------|------------|-------------|-----------|----------|
| C          | C        |            | I              | C             | C          | I        | C          | C        | C       | C        | C         | C               | I         | C        | C          | I           | C         | I        |

C: compatible; Blank: not tested; I: incompatible.

used, morphine was the most often prescribed drug (98%), followed by haloperidol (90%), furosemide (69%), and metoclopramide (44%), among others. Still in this article, the physicians were questioned as to the method used to validate the information, and 70% responded that they prescribed and validated the prescription with other medical colleagues, 32% validated with the pharmacy service of the hospital, and only 22% consulted literature.\(^{(17)}\)
Most classes of medications already in use for this route are opioids, antibiotics, antiemetics, and sedatives. Chart 3 shows some information related exclusively to medications that have already been reported in literature regarding use of hypodermoclysis.

In addition to these drugs cited on the table, there are other papers that report the use of other antimicrobials, such as ertapenem, amikacin, gentamicin, and teicoplanin, but these articles still contain limited information and apparently demonstrate equivalence when compared to the usual routes, although the numbers of patients used were very small.\(^\text{(15)}\)

A large part of the adverse reactions mentioned in the articles occurred due to inadequate use, such as for example, unsuitable puncture sites, medication inappropriate for that route of administration, inadequate dilution, and lack of rotation of puncture site (change every 96 hours).\(^\text{(11)}\)

By means of this research, we noted that the information related to the form of preparation and administration of medications is not yet standardized. Therefore, we must evaluate the patients’ conditions before indicating the administration route, and if there are other drugs or even solutions that are already being administered by the subcutaneous route, such as a saline solution, for example. We should also remember that the limit of fluids for infusion over a period of 24 hours cannot surpass 3,000mL divided into two different puncture sites (1,500mL at each puncture every 24 hours).\(^\text{(1,2,6,10)}\) This issue may be minimized since one or more drugs may be given by a single infusion system.

Chart 4 presents information related to compatibility among a few medications.\(^\text{(16,18)}\)

**DISCUSSION**

By means of the results found, we observed that the hypodermoclysis technique is a safe, effective, low cost, and easily applicable methodology\(^\text{(5,12)}\) that seems to bring some benefits.\(^\text{(1-4,8-11,14,16)}\)

However, there are still few original studies available on this topic, especially those that include the administration of medications; the working samples located were small, making it difficult to reach a definition as to the efficacy in use of these medications, which also was made evident by a few authors in their studies.\(^\text{(13,15)}\) The original studies used to compose this project focused on issues related to hydration, especially in the elderly.\(^\text{(2,6,9,10,12)}\)

Of the medications already indicated and commonly prescribed for the subcutaneous route, as was reported in one of the studies, most are prescribed primarily based on clinical practice more than on literature per se.\(^\text{(17)}\) Additionally, their form of administration ends up being in accordance with its intravenous use, since until now, the most appropriate form for preparation and administration to the patients has not yet been established; however, in literature, there is information that recommends a dilution of 1mL of medication to 1mL of diluent.\(^\text{(16)}\) Nevertheless, this information is still not a consensus for the use of all the drugs prescribed, as each one of them has their own profile regarding dilution, stability, pH, and these issues may be fundamental in order to avoid adverse events.

If the technique is not applied appropriately, it may cause problems for the patient as described in the results of this article. In this sense, instead of bringing the possible benefits by the technique, it causes more harm.

Of the 17 articles used, only one paper did not cover specific information as to the technique. This one sought to know what the level of knowledge is in a nursing team as to the technique, a fact that called our attention, since many nurses who answered the questionnaire (71%) were not familiar with the method.\(^\text{(4)}\)

This reinforces the idea that due to scarce availability of information in literature, or availability of repeated information, the technique is not amply made known, and this profile of medical prescription cased great difficulty for the pharmacist and the accompanying team in giving quality orientation so that there is safe management of the techniques of preparation and administration of drugs using the subcutaneous route.

The chart drawn up on the compatibilities shows some possibilities of optimizing puncture sites, as well as volumes of administration, which are capable of providing greater comfort for the patient due to less patient manipulation.

The greatest difficulty in this study was locating information related to the method of preparation and the time of administration of the medications, as was cited in the results, in which only five described some form of preparation and administration of medications.\(^\text{(7,11,13,16,17)}\)

The pharmaceutical industry should, on the other hand, invest and prepare studies focused on this administration technique. This can become a distinguishing factor on the market, since such a technique is geared towards patients under Palliative Care and the elderly, as these patients, on the other hand, present with reduced muscle mass, difficulty in puncturing peripheral accesses, and difficulties in swallowing.

New studies could be prepared in a considerable portion of a specific population, in order to also construct
a safety profile for the patient and for the medication itself.

CONCLUSION

The complication of this information may direct the pharmacist, as well as the medical and nursing teams in evaluating the medications to be given by hypodermoclysis, in this way offering a guarantee of therapy success and patient safety, besides decreasing risks of adverse events related to administration by such a route.

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