Brief Report

Pediatric Palliative Care at Home: A Prospective Study on Subcutaneous Drug Administration

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Abstract

Context. The subcutaneous route is a useful alternative for drug administration in palliative care. Although there is scientific evidence on its use in adult patients, the literature in pediatric palliative care is almost nonexistent.

Objectives. To describe the experience of a pediatric palliative care unit (PPCU) with in-home subcutaneous drug administration symptom control.

Methods. Prospective observational study of patients receiving home-based subcutaneous treatment administered as part of a PPCU treatment regimen over 16 months. Analysis includes demographic and clinical variables and treatment received.

Results. Fifty-four different subcutaneous lines were inserted in the 15 patients included, mainly in the thigh (85.2%). The median time of needle in situ was 5.5 days (range: 1−36 days). A single drug was administered in 55.7% of treatments. The most frequently used drugs were morphine chloride (82%) and midazolam (55.7%). Continuous subcutaneous infusion was the predominant administration route (96.7%), with infusion rates oscillating between 0.1 mL/h and 1.5 mL/h. A statistically significant relationship was found between the maximum infusion rate and induration onset. Of the 54 lines placed, 29 (53.7%) had an associated complication requiring line removal. The primary cause for removal was insertion-site induration (46.3%). Subcutaneous lines were mainly used to manage pain, dyspnea, and epileptic seizures.

Conclusion. In the pediatric palliative care patients studied, the subcutaneous route is most frequently used for administering morphine and midazolam in continuous infusion. The main complication was induration, especially with longer dwell times or higher infusion rates. However, further studies are required to optimize management and prevent complications. J Pain Symptom Manage 2023;66:e319−e326.

Key Words
Pediatrics, supportive care, symptom management, drug administration, subcutaneous infusions, home care services, hospital-based

Key Message

This prospective observational study describes the experience of a pediatric palliative care unit in using subcutaneous drug administration for symptom control in home care. The results indicate that the subcutaneous route is a safe option in home settings. The primary cause for device removal is induration of the insertion area.

Introduction

Children with life-limiting diseases require palliative care from a multidisciplinary approach.[1−3] Whenever possible, measures should be taken to provide care in the home, as stated in pediatric palliative care quality standards.[3] Symptom management is particularly important in these patients due to the complex nature of the diseases affecting them.[3−4]

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Enteral drug administration is the route of choice in palliative care. However, when this means of delivery is limited by the presence of vomiting, nausea, dyspnea, neurological conditions, impaired consciousness, intestinal obstruction, or other circumstances, alternative routes such as intravenous, rectal, intramuscular, sublingual, or transdermal administration should be considered. However, these are not entirely free of drawbacks.[5–7] When patients receive care in the home setting, the administration route should be selected rigorously. Intravenous drug delivery is not a viable option in the home setting, since managing intravenous devices requires trained personnel as complications occur frequently, and patients receiving therapy through this route have more limited autonomy.[6] Therefore, the subcutaneous (SC) route is a good alternative, as it is equally effective as intravenous delivery and is also less invasive.[5–6]

There is scientific evidence on the indications, advantages, disadvantages, and contraindications of subcutaneous drug delivery in adult palliative care,[6–8] although the literature concerning pediatric palliative care (PPC) is virtually nonexistent.

Multiple symptoms presented by adult patients can be managed with subcutaneous drug administration, such as pain, agitation, nausea/vomiting, epileptic seizures, dyspnea, dehydration, etc.[6,9] However, the drugs used in palliative medicine are often not approved for subcutaneous delivery, thus requiring for them to be used under off-label conditions.[10–13] To compensate for this, published tables provide recommendations on various drugs delivered using the subcutaneous route,[14–17] and some authors have performed studies that specifically assess the tolerability, efficacy, and safety of certain drugs when delivered subcutaneously.[18,19] In addition, mild or moderate dehydration in adult patients can be successfully managed with subcutaneous delivery.[20–24] However, this topic remains controversial, and candidates for subcutaneous treatment must be assessed on a case-by-case basis.[24–27]

The subcutaneous route is a safe alternative for the delivery of fluids and medication,[6,8–9,27,28] though it is not entirely free of complications.[6–8,29–30] Complications which are more commonly addressed in research on adult patients, mostly consist of redness, pain, induration, or hematoma.[8] These adverse effects tend to be managed by changing the insertion site, massaging the area, or reducing the rate of infusion, among other measures.[6] Differences in complications have been reported based on needle type, dwell time, and the drug combination administered.[30]

Despite the potential for these local complications, subcutaneous drug delivery is not only safe, but is also less burdensome for patients; this route of therapy requires no highly specific care and can be provided in the home under the supervision of properly trained informal caregivers.[23,31] Subcutaneous administration enables symptom management and patient hydration in the home setting, which reduces the number of hospital admissions and may increase the quality of life of patients. However, scant evidence from the pediatric population has been published to date, which may lead to underuse of subcutaneous delivery in children despite the benefits offered.

Reports of subcutaneous drug delivery in child patients include the review by Pouvreau et al.[32] in neonatal palliative care, which includes a number of protocols for symptom management (i.e., analgesia, anxiolysis, sedation) through subcutaneous access. The study highlights the need for research aimed at defining the pharmacogenetics, pharmacodynamics, and treatment modalities of subcutaneous administration in this population of patients. For their part, Harris et al.[33] describe subcutaneous administration of midazolam to manage epileptic seizures in child palliative-care patients. Smith et al.[34] present a case of subcutaneous hydration in PPC, concluding that subcutaneous fluid management is a valid option in these patients; these authors review the indications, contraindications, complications, and other important issues to consider in subcutaneous hydration. Other research has reported successful subcutaneous hydration in children, although outside the palliative care setting.[35,36]

Owing to the absence of data on this issue, analyses of the use of subcutaneous drug therapy in pediatrics are of particular interest. This study describes the experience of a pediatric palliative care unit (PPCU) in using subcutaneous drug delivery for the management of symptoms in pediatric patients in the home.

Methods

Study Setting and Criteria

A prospective observational study was performed over 16 months (January 2020–April 2021) in the PPCU of a university children's hospital in Madrid, Spain, known as the Madrid Pediatric Palliative Care Unit (MPPCU). The MPPCU is an interdisciplinary clinical unit made up of a team of pediatricians, nurses, social workers, psychologists, and a provider of spiritual support. A pharmacist belonging to the unit provides support to ensure rational, safe, and effective use of drugs through daily approval of prescribed treatments. The MPPCU treats patients with palliative needs across different care levels and in a way that adapts to the stage of the disease in each individual, including outpatients, inpatients, and in the home. In home settings, the clinical team offers care 24 hours a day, seven days a week (telephone and face-to-face depending on patient needs), in addition to scheduled home visits,

which can be daily or weekly depending on the needs of the children.

The study included those patients treated as part of a home-care program. All were undergoing subcutaneous symptom management, and parents or legal guardians gave previous informed consent to participate. Those patients in whom the SC infusion device had been inserted by a health professional not belonging to the MPPCU were excluded.

Data Collection

We collected the following variables for each patient:

- *Clinical and demographic variables*: sex, age, baseline diagnosis according to the 10th version of International Classification of Diseases (ICD-10) and the ACT (Association for children with life-threatening conditions and their families) grouping, which classifies child candidates for palliative care into four categories based on the type of disease and the speed with which the disease worsens.[37]
- *Variables related to the SC infusion device:* date of insertion, dwell time, type of needle, reason for device removal, and device-related complications.
- *Variables related to the drug treatment:* treatment indication; drugs administered, drug volume, and type of diluent (if any); route of administration (bolus, continuous/intermittent infusion); infusion rate (if applicable); and infusion device.

Data were gathered for all devices carried by a given patient; some patients were outfitted with more than one, and in some cases different drugs or drug combinations were administered by each device. A drug combination was considered any mixture of drugs within the same infusion bag or syringe and infused simultaneously. Mixtures of the same components (same drug combination) but in different concentrations were considered different items for the purpose of analysis.

Data were collected by MPPCU staff belonging to the research team to limit variability. Data on clinical and demographic variables were obtained from electronic medical records. Unit nurses administered care for study patients in the home in accordance with the usual practice of the MPPCU and carried out comprehensive follow-up of all aspects related to drug administration. According to routine unit practices, nurses in the MPPCU are responsible for inserting the device, preparing the medication, programming the infusion pump, detecting possible complications, and training caregivers to administer boluses through the pump. The unit physician is charged with prescribing drug treatment to manage symptoms, and the pharmacist approves these prescriptions and issues reports on the stability and compatibility of drugs administered subcutaneously. The frequency of home visits by the care team to monitor patients varied according to the needs of each child; these ranged from daily visits to visits two to three times weekly.

Data on medication-related variables were collected jointly by the unit's pharmacist and nurse.

Statistical Analysis

Statistical analysis was performed with IBM SPSS© Statistics V26 software. Quantitative variables were described as median and interquartile range (IQR) owing to their asymmetrical distribution; categorical variables were described using frequency distribution. Relationships between variables were analyzed via Fisher exact test as well as non-parametric tests such as the Mann-Whitney U test, Kruskal–Wallis test, or Spearman correlation coefficient, as applicable. Statistical significance was set at $P \leq 0.05$.

Ethics Approval

This study was approved by the local ethics committee (Hospital Universitario Infantil Niño Jesús). The study was conducted in accordance with the guidelines of the Declaration of Helsinki and complies with current legislation on data protection and patient autonomy. Informed consent was obtained from the parents or caregivers of patients. Patient files were processed anonymously.

Results

Characteristics of the Study Population

During the study period, 16 patients undergoing home care required insertion of an SC device. In one patient, the line was inserted and follow-up was performed in another center; as a result, the patient was excluded. Thus, a total of 15 patients were included. Their characteristics are described in Table 1.

SC Treatment Administered

During the study period, a total of 54 different SC lines were inserted. The median number of devices inserted per patient was one (IQR: 1–3) and the maximum number placed was 17 ($n = 1$).

The SC injection site in most patients was the thigh (85.2%) (Table 2). The median dwell time was 5.5 days (IQR: 2–14), with a minimum dwell time of one day and a maximum of 36 days. The causes for device removal were mainly induration at the insertion site (46.3%), death (16.7%), and change to an intravenous route (13.0%) (Table 2). In 38 cases (70.4%), SC line-removal required insertion of a new route of parenteral administration: in 31 cases (81.6%) a new SC device was placed, and in seven (18.4%) the SC line was switched to intravenous administration.

Table 1
Characteristics of the Population Studied

Variable	*N* (%)
Sex	
Male	9 (60%)
Female	6 (40%)
Age (yrs)	
Median age (IQR: P_{25}–P_{75})	7 (1.8–16)
Minimum – maximum	0.5–24
Newborn (0–28 d)	0 (0%)
Infant (1–23 mo)	3 (20%)
Preschool (2–6 yrs)	3 (20%)
Primary school (6–12 yrs)	2 (13.3%)
Adolescent (12–18 yrs)	5 (33.3%)
Adult (≥ 18 yrs)	2 (13.3%)
Baseline diagnosis (ICD-10)	
Childhood cerebral palsy (G80.0)	5 (33.3%)
Epilepsy and generalized epilepsy syndromes (G40.3–G40.4)	4 (26.7%)
Glutaric aciduria type II (E71.3)	1 (6.7%)
Cri-du-chat syndrome (deletion on chromosome 5) (Q93.4)	1 (6.7%)
Neurofibromatosis (Q85.0)	1 (6.7%)
Acute lymphoblastic leukemia (C91.0)	1 (6.7%)
Burkitt's lymphoma (C83.7)	1 (6.7%)
Malignant tumor of the brain (C71.9)	1 (6.7%)
ACT group	
Group 1	3 (20%)
Group 3	3 (20%)
Group 4	9 (60%)

Twenty-nine complications were observed in the 54 devices inserted (53.7%). All complications occurred at the insertion site and caused no clinically significant repercussions.

The most frequently detected complication was induration (25/29; 86.2%); others were recorded, although with a much lower frequency (Table 2).

No statistically significant relationship was found between the presence of induration and patient age (Mann-Whitney U test; $p = 0.71$), though a significant relationship was found between SC device dwell time and the development of induration (Mann-Whitney U test; $p = 0.034$). Thus, the SC devices removed due to induration were in use the longest.

Table 2
Descriptive Characteristics of the SC Devices Placed and, Where Applicable, Reasons for Removal

Variable	*N* (%)
SC route location	
Thigh (anterolateral side)	46 (85.2%)
Deltoid	4 (7.4%)
Infraclavicular area	3 (5.6%)
Abdomen	1 (1.8%)
Type of needle	
SC butterfly	52 (96.3%)
Insuflon	2 (3.7%)
Reasons for removal	
Induration [a]	25 (46.3%)
Death	9 (16.7%)
Change to another route (intravenous)	7 (13.0%)
Effective symptom control	4 (7.4%)
Removed by the patient	4 (7.4%)
Expelled due to hypertonia [a]	2 (3.7%)
Bending[a]	1 (1.8%)
Pain in device insertion area [a]	1 (1.8%)
Unknown	1 (1.8%)

[a]Reasons for removal that were regarded as complications in this study.

Description of the Pharmacological Treatments Administered by SC Infusion

Sixty-one pharmacological treatments were administered subcutaneously, delivering the following drugs: morphine, midazolam, haloperidol, clonidine, and dextrose 5% in sodium chloride 0.9% (D5NS), either as monotherapy or in combination (mixtures of two or three components). Slightly more than half of the treatments administered subcutaneously (55.7%) consisted of a single drug (Table 3).

The most frequently administered drugs were midazolam (administered to 73.3% of patients ($n = 11$) and involved in 82% of total treatments ($n = 50$)) and morphine (administered to 80% of patients ($n = 12$) and involved in 55.7% of total treatments ($n = 34$)). Other less frequently administered drugs were haloperidol (administered to 20% of the patients ($n = 3$) and involved in six treatments) and clonidine (administered to a single patient).

Treatment delivery, including administration of drug- and nondrug therapy (hypodermoclysis), was mainly via continuous infusion (59/61; 96.7%). Of the treatments administered via this route ($n = 58$), half ($n = 29$) were diluted with normal saline (sodium chloride 0.9%) prior to administration; the other half ($n = 29$) had no prior dilution. The rate of subcutaneous drug infusion was between 0.5 mL/h and 1.5 mL/h. Dextrose 5% in sodium chloride 0.9% ($n = 1$) was also delivered in continuous infusion at a

Table 3
Pharmacological Treatments Delivered Subcutaneously

Item	*N* (%)
Total number of pharmacological treatments delivered	61 (100%)
Number of components	
1	34 (55.7%)
- Morphine	7 (11.5%)
- Midazolam	24 (39.4%)
- Haloperidol	1 (1.6%)
- Clonidine	1 (1.6%)
- Dextrose 5% in Sodium Chloride 0.9% (D5NS)	1 (1.6%)
2	23 (37.7%)
- Morphine + midazolam	22 (36.1%)
- Morphine + haloperidol	1 (1.6%)
3	4 (6.6%)
- Morphine + midazolam + haloperidol	4 (6.6%)
Route of administration	
Continuous infusion	59 (96.7%)
Bolus	2 (3.3%)
Dosage devices	
Patient-controlled analgesia (PCA)	59 (96.7%)
Syringe	2 (3.3%)

rate of 18 mL/h for hydration of one patient. Only two patients (3.3%) underwent drug therapy by SC bolus; in both, midazolam was administered at volumes of 0.4 mL and 1 mL, respectively.

Regarding dosage devices, this study used patient-controlled analgesia (PCA) to deliver continuous infusions (96.7%), while SC boluses were administered by syringe (3.3%).

The relationship between the development of induration and the infusion rate of drugs delivered in continuous infusion was analyzed by assessing the maximum infusion rate for each treatment. A statistically significant relationship was found between the two variables ($p = 0.002$), as SC treatments with higher delivery rates had a higher frequency of induration.

Symptoms Following SC Treatment

In one case (1.6%), the SC route was used to hydrate the patient (hypodermoclysis), delivering dextrose 5%/9%; in all other cases (98.4%), subcutaneous delivery was used to manage different symptoms, mostly pain, dyspnea, and epileptic seizures (Table 4).

Discussion

The subcutaneous route has shown good results for symptom management,[8,9,32] which is a priority in palliative care. To promote drug absorption, the most widely recommended areas for device insertion are the abdominal wall, the scapular area, the chest area, and the limbs.[5–7,38–39] However, the thickness of the subcutaneous tissue is also a factor,[5] as needles for SC administration are frequently used in the pediatric population and require a minimum tissue thickness of 1 cm to 2.5 cm[38] depending on the individual treated.[39] In accordance with these recommendations and other published studies in children,[32–33] the SC devices used in this study were mainly placed in the limbs, the anterolateral thigh (85.2%), and the deltoid (7.4%). No significant difference was found between the insertion site and the onset of complications ($p = 0.884$). The SC butterfly was used in 96.3% of the events studied, which is associated with higher patient comfort and lower risk of injury, since the needle is removed after the line is placed.[40]

At present, certain controversy surrounds the dwell time of subcutaneous devices. Some authors suggest rotating the access point at least every two to seven days.[8–9,41–42] Other authors argue that the needle materials must be taken into account, as those made of Teflon are more durable.[43–44] In this study, the needle dwell time ranged from 1 to 36 days, with a median of 5.5 days; furthermore, we found that the longer the dwell time, the greater the risk of complications, especially induration ($p = 0.034$). This relationship is consistent with existing evidence, where durability limits are established to prevent the onset of complications.[8–9,41–42] However, this result will likely lead to future pediatric research aiming to set more concrete safety limits for subcutaneous device replacement, potentially modifying the current recommended period of between two and seven days.[41–42]

Our results reveal that the most frequently used drugs were midazolam (82% of all treatments) and morphine (55.7%). Midazolam is the benzodiazepine of choice in subcutaneous administration owing to its excellent tolerance and short half-life.[39] In pediatric care, subcutaneous midazolam is of interest for both the management of epileptic seizures[33] and to treat symptoms in the final stages of life.[32,45] Ample evidence exists on the use and safety of subcutaneous morphine administration,[28] a commonly administered drug in children.[32,45–46]

In 96.7% of the cases studied, midazolam and morphine were delivered in continuous infusion by PCA system at an infusion rate of between 0.1 mL/h and 1.5 mL/h. Though this advanced technological resource is not available in every clinical context, it is safe and effective in pediatric palliative home care.[47]

Table 4
Drugs Used for Symptom Management

Symptom	Number of Patients Presenting the Symptom	Number of Times the Drug was Used for Each Symptom[a]	Drug Used in Management (*N*; %)
Pain	8 (53.3%)	27 (29.3%)	Morphine ($n = 27$; 100%)
Dyspnea	6 (40%)	12 (13.0%)	Morphine ($n = 7$; 58.3%)
			Midazolam ($n = 5$; 41.7%)
Epileptic seizures	4 (26.7%)	41 (44.6%)	Midazolam ($n = 41$; 100%)
Neurological irritability	2 (13.3%)	5 (5.4%)	Midazolam ($n = 3$; 60%)
			Haloperidol ($n = 2$; 40%)
Nausea / vomiting	2 (13.3%)	4 (4.3%)	Haloperidol ($n = 4$; 100%)
Dystonia breakdown	1 (6.7%)	1 (1.1%)	Clonidine ($n = 1$; 100%)
Sedation	1 (6.7%)	1 (1.1%)	Midazolam ($n = 1$; 100%)
Dehydration − Hypodermoclysis	1 (6.7%)	1 (1.1%)	Dextrose ($n = 1$; 100%)

[a]Treatments included ($n = 61$) consisted of one, two, or three different components (drugs), which means that a **total 92 drugs** were used as indicated. The indications for which each drug was used are presented in this column.

The data reported here suggest that in the field of PPC, the infusion rate must be considered to prevent subcutaneous route-associated complications, especially in the case of induration, where a greater incidence was observed at higher infusion rates. This relationship was statistically significant ($p = 0.002$) for infusion rates of between 0.1 mL/h and 1.5 mL/h; this may mark a starting point for future pediatric research, as there are no existing studies on the most appropriate rate in children.[48] The infusion rates found in this study in children (0.1−1.5 mL/h) differed markedly from the rates reported for the adult population.[6,49–50]

Redness, pain, induration, and hematoma are the most frequent complications reported in the literature, both in adults[6,8] as well as in children.[34] Similarly, in our study induration was the most common complication, leading to removal of 46.3% of the devices placed. As Nakayama et al.[51] mention, it is important to prevent and manage this complication, since it could be related to decreased bioavailability at the insertion point.

In contrast, pain caused only 1.8% of device removals. This may be lower than the true rate, given the patients' inability to clearly articulate their experience of pain. Although specific scales have been designed to assess pain in patients with cognitive decline and/or traumatic brain injury,[52–54] it must be kept in mind that in the absence of other symptoms such as redness, inflammation, or induration, the task of assessing pain becomes more complex, as care providers must determine whether the pain is secondary to the SC access device or has another source. Moreover, assessing pain through nonverbal signs is difficult in patients nearing the end of life due to their varying states of consciousness.

Limitations and Strengths of the Study

This study's main limitation is the small sample size, which means the results should be interpreted with caution. Future research could benefit from a multicenter approach grouping a larger number of individuals.

PPC is a burgeoning discipline despite the relatively small number of patients. As a result, there is scant information on this patient population and further research is required.

As described above, subcutaneous administration can be safe and useful in pediatric palliative-care patients. Currently, however, this evidence remains scarce, possibly leading to underuse.

Conclusions

This study supports the use of the subcutaneous route as a safe and useful home-care alternative for the management of child patients with symptoms such as pain, dyspnea, or epileptic seizures.

Most of the pharmacological treatments administered in this study delivered a single drug, the most common being midazolam and morphine. These treatments were administered by continuous infusion more frequently than by bolus, and the infusion rates were much lower than those recommended in the adult population. The main cause for device removal was device-related complications, all located at the insertion point. The main complication detected was induration at the insertion point, associated with longer needle dwell times and a higher drug infusion rate.

Authors' Contributions

All authors have made substantial contributions to the conception of the work, acquisition, data collection, analysis, interpretation of data, drafting the article, and approved the final version to be published.

Declaration of Competing Interest

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References

1. Himelstein BP. Palliative care in pediatrics. Anesthesiol Clin North Am 2005;23:837–856.

2. Organización Mundial de la Salud. Cuidados paliativos [Internet]. Ginebra (Suiza): Organización Mundial de la Salud; 2020. [Accessed May 30, 2021]. Available from: https://www.who.int/es/news-room/fact-sheets/detail/palliative-care.

3. Benini F, Papadatou D, Bernadá M, et al. International standards for pediatric palliative care: from IMPaCCT to GO-PPaCS. J Pain Symptom Manage 2022;63:e529–e543.

4. Brenner M, Kidston C, Hilliard C, et al. Children's complex care needs: a systematic concept analysis of multidisciplinary language. Eur J Pediatr 2018;177:1641–1652.

5. Pontalti G, Rodrigues ES, Firmino F, et al. Subcutaneous route: second option in palliative care. Revista HCPA 2012;32:199–207.

6. Gallardo Avilés R, Gamboa Antiñolo F. Uso de la vía subcutánea en cuidados paliativos, 4. Madrid (Spain): Sociedad Española de Cuidados Paliativos (SECPAL); 2013. p. 1–48. https://www.secpal.org/uso-de-la-via-subcutanea-en-cuidados-paliativos-ultima-monografia-secpal/.

7. Ruiz Márquez MP. Programa regional de cuidados paliativos. Guía clínica vía subcutánea, usos y recomendaciones. Observatorio Regional de Cuidados Paliativos de Extremadura 2010. [Accessed May 30, 2021]. Available from: https://saludextremadura.ses.es/paliex/subcutanea.

8. Bartz L, Klein C, Seifert A, Herget I, Ostgathe C, Stiel S. Subcutaneous administration of drugs in palliative care:

results of a systematic observational study. J Pain Symptom Manage 2014;48:540–547.

9. Justad M. Continuous subcutaneous infusion: an efficacious, cost-effective analgesia alternative at the end of life Home Healthc Nurse. 2009;27:140-7.

10. Wernli U, Dürr F, Jean-Petit-Matile S, Kobleder A, Meyer-Massetti C. Subcutaneous drugs and off-label use in hospice and palliative care: a scoping review. J Pain Symptom Manage 2022;64(5):e250–e259.

11. Jensen JJ, Sjøgren P. Administration of label and off-label drugs by the subcutaneous route in palliative care: an observational cohort study. BMJ Support Palliat Care 2022;12:e723–e729.

12. García-López I, Cuervas-Mons Vendrell M, Martín Romero I, de Noriega I, Benedí González J, Martino-Alba R. Off-label and unlicensed drugs in pediatric palliative care: a prospective observational study. J Pain Symptom Manage 2020;60:923–932.

13. Hagemann V, Bausewein C, Remi C. Drug use beyond the licence in palliative care: A systematic review and narrative synthesis. Palliat Med 2019;33:650–662.

14. Matoses Chirivella C, Rodríguez Lucena FJ, Sanz Tamargo G, Murcia López AC, Morante Hernández M, Navarro Ruiz A. Administración de medicamentos por vía subcutánea en cuidados paliativos [Subcutaneous drug administration in palliative care]. Farm Hosp., 39; 2015. Spanishp. 71–79.

15. Domínguez Álvarez R, Calderón Carrasco J, García Colchero f, et al. Farmacología en cuidados paliativos. Vías de administración, mezclas, efectos secundarios frecuentes, normas básicas para el control de síntomas. Rev ROL Enferm 2015;38:54–65.

16. Dickman A, Bickerstaff M, Jackson R, Schneider J, Mason S, Ellershaw J. Identification of drug combinations administered by continuous subcutaneous infusion that require analysis for compatibility and stability. BMC Palliat Care 2017;16:22.

17. Rose M, Currow DC. The need for chemical compatibility studies of subcutaneous medication combinations used in palliative care. J Pain Palliat Care Pharmacother 2009;23:223–230.

18. Leheup BF, Ducousso S, Picard S, Alluin R, Goetz C. Subcutaneous administration of paracetamol-Good local tolerability in palliative care patients: An observational study. Palliat Med 2018;32:1216–1221.

19. Jackson K, Ashby M, Howell D, et al. The effectiveness and adverse effects profile of "burst" ketamine in refractory cancer pain: The VCOG PM 1-00 study. J Palliat Care 2010;26:176–183.

20. Chanthong P, Siriwattanakul S, Srion C. Comparison of feasibility between hypodermoclysis and intravenous hydration among palliative care patients in Thailand. Int J Palliat Nurs 2022;28:308–312.

21. Coelho TA, Wainstein AJA, Drummond-Lage AP. Hypodermoclysis as a Strategy for patients with end-of-life cancer in home care settings. Am J Hosp Palliat Care 2020;37:675–682.

22. Vidal M, Hui D, Williams J, Bruera E. A prospective study of hypodermoclysis performed by caregivers in the home setting. J Pain Symptom Manage 2016;52:570–574. e9.

23. Remington R, Hultman T. Hypodermoclysis to treat dehydration: a review of the evidence. J Am Geriatr Soc 2007;55:2051–2055.

24. Danielsen MB, Andersen S, Worthington E, Jorgensen MG. Harms and benefits of subcutaneous hydration in older patients: systematic review and meta-analysis. J Am Geriatr Soc 2020;68:2937–2946.

25. Agar MR, Chang S, Amgarth-Duff I, et al. Investigating the benefits and harms of hypodermoclysis of patients in palliative care: a consecutive cohort study. Palliat Med 2022;36:830–840.

26. Cabañero-Martínez MJ, Velasco-Álvarez ML, Ramos-Pichardo JD, Ruiz Miralles ML, Priego Valladares M, Cabrero-García J. Perceptions of health professionals on subcutaneous hydration in palliative care: A qualitative study. Palliat Med 2016;30:549–557.

27. Cabañero-Martínez MJ, Ramos-Pichardo JD, Velasco-Álvarez ML, García-Sanjuán S, Lillo-Crespo M, Cabrero-García J. Availability and perceived usefulness of guidelines and protocols for subcutaneous hydration in palliative care settings. J Clin Nurs 2019;28:4012–4020.

28. Broadhurst D, Cooke M, Sriram D, Gray B. Subcutaneous hydration and medications infusions (effectiveness, safety, acceptability): a systematic review of systematic reviews. PLoS One 2020;15:e0237572.

29. Guedes NAB, de Melo LS, Santos FBO, et al. Complications of the subcutaneous route in the infusion of medications and solutions in palliative care. Revista da Rede de Enfermagen do Nordeste 2019;20:1–9.

30. Mitchell K, Pickard J, Herbert A, Lightfoot J, Roberts D. Incidence and causes for syringe driver site reactions in palliative care: a prospective hospice-based study. Palliat Med 2012;26:979–985.

31. Gabriel J. Achieving successful subcutaneous access in palliative patients. Int J Palliat Nurs 2018;24:282–287.

32. Pouvreau N, Tandonnet J, Tandonnet O, Renesme L. Utilisation de la voie sous-cutanée en soins palliatifs néonatals : revue de la littérature et enquête de pratique en France [Use of subcutaneous route for comfort care in neonatal palliative population: Systematic review and survey of practices in France]. Arch Pediatr 2017;24:850–859.

33. Harris N, Baba M, Mellor C, Rogers R, Taylor K, Beringer A, Sharples P. Seizure management in children requiring palliative care: a review of current practice. BMJ Support Palliat Care 2020;10(3):e22.

34. Smith A, Jane Brimble M. Use of subcutaneous fluids in palliative care with children: a case study. Nurs Child Young People 2020;32:26–30.

35. Saganski GF, de Souza Freire MH. Safety and effectiveness of hypodermoclysis compared to intravenous fluid infusion for rehydrating children with mild to moderate dehydration: a systematic review protocol. JBI Database System Rev Implement Rep 2019;17:1270–1276.

36. Kuensting LL. Comparing subcutaneous fluid infusion with intravenous fluid infusion in children. J Emerg Nurs 2013;39:86–91.

37. Chambers L. A Guide to Children's Palliative Care. 4th ed. Bristol (UK): Together for Short Lives; 2018.

38. Schoenbeck SL, McBride K. Hypodermoclysis: easy, safe, cost-effective. J Pract Nurs 2010;60:7–8.

39. Duems-Noriega O, Ariño-Blasco S. Subcutaneous fluid and drug delivery: safe, efficient and inexpensive. Rev Clin Gerontol 2015;25:117–146.

40. Gabriel J. Sharps injuries and their prevention: what the new European legislation may mean for palliative care services. Int J Palliat Nurs 2012;18:218–223.

41. Gorski L. Standard 64: continuous subcutaneous access devices. J Infus Nurs 2009;32:185–186.

42. Infusion Nurse Society. Infusion nursing standards of practice. J Infus Nurs 2011;34(Suppl 1):S1–S109.

43. Ross JR, Saunders Y, Cochrane M, Zeppetella G. A prospective, within-patient comparison between metal butterfly needles and Teflon cannulae in subcutaneous infusion of drugs to terminally ill hospice patients. J Palliat Med 2002;16:13–16.

44. Carrión Torre M. Subcutaneous infusion: non-metal cannulae vs metal butterfly needles. Br J Community Nurs 2002;7:365–369.

45. Marquis MA, Daoust L, Villeneuve E, Ducruet T, Humbert N, Gauvin F. Clinical use of an order protocol for distress in pediatric palliative care. Healthcare (Basel) 2019;7:3.

46. Baumann F, Hebert S, Rascher W, Woelfle J, Gravou-Apostolatou C. Clinical characteristics of the end-of-life phase in children with life-limiting diseases: retrospective study from a single center for pediatric palliative care. Children 2021;8:1–10.

47. Nijland L, Schmidt P, Frosch M, et al. Subcutaneous or intravenous opioid administration by patient-controlled analgesia in cancer pain: a systematic literature review. Support Care Cancer 2019;27:33–42.

48. Mitrea N, Mosoiu D, Vosit-Steller J, Rogozea L. Evaluation of the optimal positioning of subcutaneous butterfly when administering injectable opioids in cancer patients. Clujul Med 2016;89:486–492.

49. Dychter SS, Gold DA, Haller MF. Subcutaneous drug delivery: a route to increased safety, patient satisfaction, and reduced cost. J Infus Nurs 2012;35:154–160.

50. López JH, Reyes-Ortiz CA. Subcutaneous hydration by hypodermoclysis. Rev Clin Gerontol 2010;20:105–113.

51. Nakayama H, Echizen H, Ogawa R, Akabane A, Kato T, Orii T. Induration at injection or infusion site may reduce bioavailability of parenteral phenobarbital administration. Ther Drug Monit 2017;39(3):297–302.

52. Malviya S, Voepel-lewis T, Burke C, MMerkel S, Tait A. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. Paediatr Anaesth 2006;16:258–265.

53. Crellin D, Harrison D, Santamaria N, Babl F. Comparison of the psychometric proprieties of the FLACC Scales, the MBPS and the observer applied visual analogue scale used to assess procedural pain. J Pain Res 2021;14:881–892.

54. Breau LM, McGrath PJ, Camfield CS, Finley GA. Psychometric properties of the noncommunicating children's pain checklist-revised. Pain 2002;99:349–357.