Subcutaneous Administration of Drugs in Palliative Care: Results of a Systematic Observational Study

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Abstract

Context. Especially in palliative care, safe and manageable administration of medication is essential. Subcutaneous drug administration is a possible alternative, when oral intake is hampered. However, evidence for this method is rare.

Objectives. This observational study assessed the clinical practice of subcutaneous drug administration, focusing on the evaluation of local reactions or complications to further develop recommendations.

Methods. Over 14 months, patients in a specialized inpatient palliative care unit treated by the subcutaneous route were invited to participate in this clinical study. All subcutaneous medications including dosage and volume of injection, type of needles, and injection site were documented. The injection sites were systematically assessed including the subjective perceptions of patients for analysis of patient tolerability and acceptability. T-tests and Chi-squared tests of these variables were performed to calculate group differences between needles with vs. without complications ($P < 0.05$).

Results. In 120 patients, 3957 applications were administered via 243 needles. The needles were placed in thighs (38.7%) and upper arms (28.8%). Most frequently used medications were hydromorphone (59.0%), haloperidol (12.3%), and midazolam (8.3%). Complications were diagnosed most often on the third or fourth day of the needle in situ and occurred significantly more often in (fully) active patients and patients transferred or discharged at the end of treatment. The mean time of needle in situ was significantly lower (4.1 vs. 5.0 days) in complication cases than in noncomplication cases ($t$-test: $P = 0.027$).

Conclusion. The results of this study acknowledge the clinical practice of subcutaneous administration of medication as a very flexible, broadly feasible, rather
safe, and nonburdensome method. Nevertheless, this practice is not free from complications, needs appropriate nursing care, and requires standardized policies and procedures. J Pain Symptom Manage 2014;48:540–547. © 2014 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Key Words
Symptom management, palliative care, drug administration, subcutaneous

Introduction
In palliative and hospice care, the management of complex symptoms in terminally ill patients requires frequent administration of medications. The route of administration should be reliable and effective but preferably not burdensome for the individual patient.1

For a variety of reasons, oral intake can be hampered. Patients approaching the end of life may be unable to tolerate oral medication because of their underlying disease and/or symptoms, such as nausea, vomiting, or difficulty swallowing (dysphagia).2,3 Thus, alternative routes for the administration of medications are needed. Peripheral or central venous catheters are prone to complications and infections, and they are intended to remain in situ for only a few days, which does not allow for long-term care planning, particularly in outpatient settings.4 Also, only a minority of patients has a port catheter system implanted, and an extra operative intervention for a port installation is usually not indicated. As well, only a few medications can be administered transdermally.5

The particular situation of patients receiving palliative care demands safe and manageable alternatives to oral administration. During the past decades, the administration of medications via the subcutaneous route has been established.6 Syringe drivers are routinely used for the subcutaneous infusion of drugs for pain and symptom control in palliative care.7 Using a continuous subcutaneous catheter offers several advantages over oral and intravenous routes with regard to patients’ comfort and quality of care.8 The subcutaneous route usually is associated with a lower infection risk than intravenous catheter systems, and its use prevents patients from receiving repeated injections and associated feelings of discomfort.9,10 However, complications arising from mechanical problems, dislocation, or local reactions at the infusion site are recognized.7 Aside from that, most drugs used for symptom management in palliative care are not licensed for subcutaneous use in Germany.

Numerous researchers have investigated the application of single drugs,11 compatibility12,13 and local tolerability of certain drugs,14 and use of specific subcutaneous devices15,16 in different care settings. However, an overview of the clinical practice of subcutaneous drug administration is still missing, and especially risk factors and complications17 have not yet been determined comprehensively.4,18

To address this gap in the evidence, this study aims to systematically assess and describe the clinical practice of noncontinuous subcutaneous bolus drug administration in an inpatient palliative care unit in Germany, focusing on patients’ acceptability, tolerability, factors influencing complications at the infusion site, and limiting factors for this method. This investigation seeks to improve clinical practice by identifying factors influencing the occurrence of complications and discomfort.

Methods
Study Plan
Between October and December 2011, a pilot study was performed to test the documentation sheets that were developed for this study. Feedback from nurses was used to adapt items as well as simplify and fine-tune documentation needs.

The adapted documentation sheets were then used for data recording in a systematic, prospective, and observational study from January 2012 until February 2013. Additionally, the core documentation form of the German Hospice and Palliative Care Evaluation was used to assess sociodemographic and epidemiological data.19,20
Study Design and Patient Recruitment

In clinical care, the subcutaneous needle (venipuncture set) is placed beneath and almost parallel to the skin surface. The direction of puncture is upward. The venipuncture set is padded with a sterile gauze compress and fixed with a 12 cm transparent film dressing. The tube connected to the subcutaneous needle is fixed on the skin with a patch to prevent dislocation. After each injection, 0.5 mL of 0.9% sodium chloride solution is given to ensure that the drug volume is fully administered and to rinse the catheter. Common guidelines for clinical practice of subcutaneous treatment define a maximum length of up to 72 hours or longer in situ if there is no pain, swelling, or erythema at the insertion site.21

All consecutive patients treated in the specialized inpatient palliative care unit who received medication subcutaneously in routine clinical practice were invited to participate in this clinical study. A trained medical student assistant informed the potential study participants or their legal representatives about the study aims, voluntary participation, procedures, and protocol. The written consent of enrolled patients or their legal representatives was obtained.

Aside from assessing the subjective feeling of patients during subcutaneous drug injection, no additional study measures were done. The study was approved by the local ethics committee in July 2011 (Reference Number 4494).

Data Collection

During the patients’ hospital stay, nurses were requested to continuously record all intermittent subcutaneous bolus administrations of medications applied via a permanent needle on a specifically developed documentation sheet. Date, location of site, and type of needle were documented. For each subcutaneous drug administration, the running number of administrations, time of administration, type of drug, dosage (in milligrams), volume (in milliliters), subjective patient feelings, and assessment by the team member during administration were systematically recorded. The documentation for use of a needle was completed when this needle was removed, because of either clinical routine or a certain indication/complication. In case of a complication, a photo of the location of the site was taken to document adverse events. One-time drug administrations in addition to the permanent needle at a different injection site were documented separately.

Additionally, patients’ mobility (fully active/mobile, mobilization with assistance possible, only positioning in bed possible, and completely disabled) and skin condition (multiple answers possible: healthy, sufficient subcutaneous fat, vulnerable skin, sparse subcutaneous fat, parchment, cachectic, edematous, hematoma, and circulatory disorder) at each possible injection site (upper arms, thighs, abdomen, or infraclavicular) were marked on a body drawing at the beginning of the treatment.

Data Analyses and Statistics

Descriptive statistics and frequencies were calculated for study population data. To identify factors influencing the occurrence of complications and discomfort, two groups were formed: subcutaneous needles with vs. without complications. Chi-squared tests and t-tests of relevant variables were performed to detect differences between these two groups (P < 0.05).

Results

Study Sample

During the 14 months of the study, 337 patients were treated in the inpatient palliative care unit. Drug administration via a subcutaneous needle was performed in 245 patients (72.7%) at some time during the inpatient stay. For various reasons, 125 patients could not be included in the study (patient not capable and no legal representative; refusal of participation; organizational losses; other reasons). Written consent for study participation was received from 120 patients (35.6%), whose data were used for further analysis.

Demographic and Disease-Related Data

Mean ± SD age of the study participants was 68 ± 13 years (range 28–91 years); 56% were females. Before admission to hospital, 69 patients (57.5%) lived with family members, 21 (17.5%) lived alone, and eight (6.7%) were
transferred from a nursing home (22 [18.3%] missing data). Mean duration of stay in the palliative care unit was 13 ± 10 days (range 1–48 days). Most study participants (87.5%) had a cancer diagnosis. Malignant neoplasms of digestive (35.0%), female genital (13.3%), and respiratory/intrathoracic organs (8.4%) or breast cancer (8.4%) were the most prevalent. Noncancer patients suffered from diseases of the nervous (4.2%), circulatory (3.3%), or digestive system (1.7%). Overall, 82.5% of all patients had Eastern Cooperative Oncology Group22 scores of 3 or 4. Eighty-four patients (70%) died, and 36 patients (30%) were discharged at the end of treatment (Table 1).

The patient group that could not be included, although drugs were given subcutaneously, did not differ in age, sex, and end of treatment (death or discharge) but only in terms of a significantly shorter inpatient stay as compared with study participants (6.3 vs. 10.1 days; t-test: P < 0.001).

Characteristics of Subcutaneous Drug Administration

Overall, 3957 applications were administered via 243 needles. The number of applications per needle ranged from 1 to 72 (mean 16.3 ± 12.9). A portion of these administrations comprised two (n = 1065; 26.9%), three (n = 147; 3.7%), or up to four (n = 22; 0.6%) different drugs given one after another. In total, 5382 drugs were given within the overall 3957 applications.

The 243 needles were placed in the thigh (38.7%), upper arm (28.8%), abdomen (18.5%), or in the infraclavicular region (9.5%) (4.5% missing data). Mainly, venipuncture sets (Venofix A®; B. Braun Medical, Inc., Melsungen, Germany) (96.7%), sets for subcutaneous infusion (Therastick 28G®; Fresenius Kabi AG, Bad Homburg, Germany) (0.8%), and closed intravenous catheters (Introcan Safety®, B. Braun Medical, Inc., Melsungen, Germany) (0.4%) were used (2.1% missing data). Skin condition was evaluated as predominantly good (83.5%), with sufficient subcutaneous fat tissue (56.3%). In some cases, the skin was described as having sparse subcutaneous fat tissue (7.0%), as being edematous (2.0%), cachectic (1.6%), or as parchment-like (0.4%).

The mean length of time in situ was 4.8 ± 2.6 days (range 1–16 days). The overall volume of injections (including the 0.5 mL of 0.9% sodium chloride after each application) per needle varied between 0.7 and 512.2 mL (mean 22.2 ± 36.8 mL). The most frequently used medications were hydromorphone (59.0%), haloperidol (12.3%), midazolam (8.3%), cyclizine (7.7%), hyoscine-N-butylbromide (4.4%), and morphine (2.2%).

Burning was the most frequent unpleasant sensation reported by patients during subcutaneous drug administration (prednisolone [n = 3; 6.1%], cyclizine [n = 36; 8.2%], hydromorphone [n = 192; 5.9%], and levomepromazine [n = 2; 5.9%]) (Table 2). Team members primarily observed signs of unpleasant sensations during administration of hyoscine-N-butylbromide (n = 7; 2.9%) and

Table 1
Demographic Data (N = 120)

<table>
<thead>
<tr>
<th>Personal data</th>
<th>Gender</th>
<th>56% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td>Mean 68 ± 13 yrs</td>
</tr>
<tr>
<td>ECOG score</td>
<td>0 (fully active)</td>
<td>3.3%</td>
</tr>
<tr>
<td></td>
<td>1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature)</td>
<td>1.7%</td>
</tr>
<tr>
<td></td>
<td>2 (ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours)</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>3 (limited self-care, confined to bed or chair more than 50% of waking hours)</td>
<td>35.0%</td>
</tr>
<tr>
<td></td>
<td>4 (completely disabled, cannot carry on any self-care, and totally confined to bed or chair)</td>
<td>47.5%</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td>Cancer</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>Noncancer</td>
<td>12.5%</td>
</tr>
<tr>
<td>Duration of care</td>
<td>Mean 13 ± 10 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range 1–48 days</td>
<td></td>
</tr>
<tr>
<td>End of treatment</td>
<td>Discharge</td>
<td>30.0%</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>70.0%</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group.
levomepromazine ($n = 1; 2.9\%$), and agitation with signs of grimacing or defense reactions with levomepromazine ($n = 1; 2.9\%$) (Table 3). Finally, most venipuncture sets were removed because of the patient’s death (32.5\%), an internal standard of maximum time in situ of seven days (30.0\%), accidental removal by patient (5.3\%), patient discharge (4.9\%), or changes in administration route (3.4\%) (3.7% missing data). Of 49 needles (20.2\%), 32 (65.3\%) were removed for one reason and 17 (34.7\%) for two simultaneous complications. Complications included redness (36.4\%), reflux of blood or tissue liquid (13.6\%), pain (12.1\%), induration (4.6\%), burning (4.6\%), dislocation (7.6\%), hematoma (3.0\%), edema/swelling (15.1\%), and needle obstruction (3.0\%).

Factors Influencing the Occurrence of Complications

In ambulatory patients, 26.3\% of the subcutaneous needles had complications. As well, complications were observed in 6.6\% of all needles placed in patients confined to bed ($P = 0.018$, Chi-squared test). Overall, 41.6\% of subcutaneous needles used in patients who were finally transferred or discharged at the end of an inpatient stay vs. 21.2\% of needles in patients who died during the study phase had led to complications ($P = 0.042$, Chi-squared test). The mean time of needle in situ was significantly lower (4.1 vs. 5.0 days) in complication cases than in noncomplication cases (t-test: $P = 0.027$). Complications were diagnosed most often on the third or fourth day of the needle in situ. Complication-free needles were used for up to 16 days (Fig. 1).

The absolute number of applications of clonidine showed a statistically nonsignificant trend toward higher complication rates ($n = 0.16$ in complication vs. $n = 0.02$ in noncomplication needles; t-test: $P = 0.057$), although no subjective complaints or negative objective assessments were documented. Two patients (51 and 66 years old) received clonidine via five needles, of which three led to complications.

### Table 2

<table>
<thead>
<tr>
<th>Subcutaneous Medication</th>
<th>No Problem, $n$ (%)</th>
<th>Burning, $n$ (%)</th>
<th>Pain, $n$ (%)</th>
<th>Missing Data, $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone ($N = 3241$)</td>
<td>3026 (93.4)</td>
<td>192 (5.9)</td>
<td>23 (0.7)</td>
<td>36 (1.1)</td>
</tr>
<tr>
<td>Haloperidol ($N = 660$)</td>
<td>629 (95.3)</td>
<td>28 (4.2)</td>
<td>3 (0.5)</td>
<td>9 (1.3)</td>
</tr>
<tr>
<td>Midazolam ($N = 465$)</td>
<td>451 (97.0)</td>
<td>13 (2.8)</td>
<td>1 (0.2)</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>Cyclizine ($N = 432$)</td>
<td>392 (90.8)</td>
<td>36 (8.3)</td>
<td>4 (0.9)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Hyoscine-Nbutylbromide ($N = 237$)</td>
<td>223 (94.1)</td>
<td>13 (5.5)</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Morphine ($N = 122$)</td>
<td>117 (95.9)</td>
<td>5 (4.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Prednisolone ($N = 49$)</td>
<td>46 (93.9)</td>
<td>3 (6.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Levomepromazine ($N = 33$)</td>
<td>31 (93.9)</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Clonidine ($N = 15$)</td>
<td>15 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (6.2)</td>
</tr>
<tr>
<td>Levomethadone ($N = 9$)</td>
<td>9 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

*Includes agitation, grimacing with pain, and defense reaction.

### Table 3

<table>
<thead>
<tr>
<th>Subcutaneous Medication</th>
<th>No Problem, $n$ (%)</th>
<th>Burning, $n$ (%)</th>
<th>Reddening, $n$ (%)</th>
<th>Others,* $n$ (%)</th>
<th>Hematoma, $n$ (%)</th>
<th>Missing Data, $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone ($N = 3239$)</td>
<td>3165 (97.7)</td>
<td>41 (1.3)</td>
<td>10 (0.3)</td>
<td>21 (0.6)</td>
<td>2 (0.1)</td>
<td>38 (1.2)</td>
</tr>
<tr>
<td>Haloperidol ($N = 662$)</td>
<td>644 (97.3)</td>
<td>8 (1.2)</td>
<td>3 (0.4)</td>
<td>7 (1.1)</td>
<td>0 (0.0)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>Midazolam ($N = 463$)</td>
<td>457 (98.7)</td>
<td>5 (1.1)</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Cyclizine ($N = 432$)</td>
<td>420 (97.2)</td>
<td>8 (1.9)</td>
<td>3 (0.7)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Hyoscine-Nbutylbromide ($N = 238$)</td>
<td>230 (96.6)</td>
<td>7 (3.0)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Morphine ($N = 129$)</td>
<td>121 (99.2)</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Prednisolone ($N = 47$)</td>
<td>46 (97.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>3 (12.7)</td>
</tr>
<tr>
<td>Levomepromazine ($N = 33$)</td>
<td>31 (94.0)</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Clonidine ($N = 13$)</td>
<td>13 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (18.7)</td>
</tr>
<tr>
<td>Levomethadone ($N = 9$)</td>
<td>9 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

*Includes agitation, grimacing with pain, and defense reaction.
No significant group differences between complication vs. noncomplication needles were found in the variables location of injection, Eastern Cooperative Oncology Group score, skin condition, number of applications (t-test: $P = 0.488$), number of different drugs administered (t-test: $P = 0.341$), overall volume of applications (t-test: $P = 0.141$), count (t-test: $P = 0.481$), and percentage (t-test: $P = 0.457$) of applications of two to four drugs in rapid succession.

**Discussion**

To our knowledge, this study is one of the first comprehensive and systematic evaluations of the clinical practice of noncontinuous subcutaneous bolus applications of drugs in an inpatient palliative care unit with a study phase of more than one year. The consideration of patients’ subjective perceptions and objective observations of nursing staff especially provides new insights into this issue.

The data on the overall treated population during the study period clearly show that pharmacological treatment of terminally ill patients via the subcutaneous route is a frequently used clinical practice in the studied service. Almost two-thirds of all patients received drugs via this route at some time during their inpatient stay. In the surveyed service, common clinical indications for the subcutaneous administration of drugs include severe nausea and emesis, pronounced pain or dyspnea, and the inability to swallow.

During development of the study design, the researchers hypothesized that probable factors influencing the occurrence of complications were the overall number of applications or the volume applied. These hypotheses have contributed to the set of variables of interest reported in this evaluation. The data analysis, however, came to the empirically derived finding that almost none of these initially suggested risk factors had a significant impact on complications. Indeed, this is a very central and important result. The results can be interpreted as a confirmation of the current practice and underline the flexibility of this method. The clinical practice of subcutaneous drug administration is practical, although not free from complications.

Data from the literature showed that in a fifth of the studied cases, the subcutaneously placed needle caused some kind of complication. Comparable findings on incidence and causes for site reactions in using syringe driver infusions for drug administration were reported by Mitchell et al. However, the complications observed in the present study occurred rather early after the needle was placed in situ, were detected immediately by the nurses, and could be easily controlled by removing the needle. None of these complications was evaluated as a severe adverse event or required specific treatment. Nevertheless, according to our findings, regular observation of the injection site is needed.

Mobility and activity of patients in the inpatient palliative care unit were identified as potential factors increasing the risk for complications. This result seems valid from clinical observations, as moving and carrying out activities of daily living may strain the tissue surrounding the injection site and lead to skin irritations and dislocation. Based on their current findings, therefore, the authors recommend monitoring injection sites in (fully) active patients during each application. One could use a Teflon cannulae rather than a metal butterfly, as Teflon cannulae were evaluated in the literature as more comfortable with a longer duration in situ until restting was necessary. The trend toward higher rates of complications in patients treated with clonidine must be interpreted cautiously; there were few available data because of the small patient group in this study.

Regarding patients’ subjective feelings during drug administration and according to
objective nursing assessments, the ratio of complaints and observed adverse effects as a result of subcutaneous drug administration was low, so that the clinical practice can be evaluated as almost nonburdensome to patients. In summary, the authors conclude from the literature and the evidence gained in this study that, in cases without complications, leaving a needle in situ for a maximum of seven days seems to be a safe practice. Application of two or more drugs in rapid succession is possible, and administration of variable volumes is a safe practice.

Study Limitations

The data analyzed here are limited to the clinical practice of one inpatient palliative care unit in Germany. This investigation does not allow a fully comprehensive overview of all drugs used in palliative care. Therefore, the findings are not generalizable to other drugs. Drugs that were not administered via a permanent subcutaneous needle did not meet the methodological requirements of this investigation and were not considered for analysis. Therefore, drugs given via a separate needle for one-time use of, for example, methylnaltrexone, octreotide, and enoxaparin, were not investigated. Continuous subcutaneous fluid infusions or administration of drugs via permanent controlled analgesia pumps also were not considered. Because some drugs were very rarely administered in this study, the results from the data should be interpreted with caution.

Although patients who could not be included in the study did not differ in demographic data from the included study participants, a possible selection bias could have taken place because more than half of the eligible patients were not enrolled in the study.

Conclusions

The results of this study acknowledge the clinical practice of subcutaneous administration of medication as a very flexible, broadly feasible, rather safe, and nonburdensome method. Further research is necessary to evaluate continuous subcutaneous fluid infusions and to systematically compare different types of needles to recommend best practice, particularly for ambulatory patients. In addition to palliative care and hospice practices, this method of drug administration possibly could be enlarged to include other medical specialties.

Disclosures and Acknowledgments

This study received an unrestricted grant from B. Braun Melsungen GmbH, Melsungen, Germany. The authors have no conflicts of interest to declare. The authors gratefully thank all the patients for their participation.

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