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TITLE:

NASAL FENTANYL ALONE PLUS BUCCAL MIDAZOLAM: AN OPEN-LABEL, RANDOMISED, CONTROLLED FEASIBILITY STUDY IN THE DYING

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ABSTRACT

INTRODUCTION

Many patients want to stay at home to die. They invariably become unable to take oral medication during their terminal phase. Symptoms are usually controlled by subcutaneous medications. There have been no studies on nasal fentanyl (NF) or buccal midazolam (BM) to control symptoms in the dying.

OBJECTIVE

To establish how best to conduct a definitive, randomised controlled trial (RCT) to determine whether NF and BM administered by families, for patients dying at home, lead to faster and better symptom control and fewer community nursing visits than standard breakthrough medication by healthcare professionals.

METHODS

This open-label mixed methods feasibility RCT compared the efficacy of NF and BM by family members to standard breakthrough medication by nurses for the terminally ill in a specialist palliative care unit. Partway through the study, a third observational arm was introduced where BM alone was used. The primary outcomes were whether recruitment and randomisation were possible, assessment of withdrawal and drop-out, and whether the methods were acceptable and appropriate.

RESULTS

Administration of NF and BM was acceptable to patients and families. Both were well tolerated. We were unable to obtain quality of life data consistently but did get time period data for dose-controlled symptoms.

CONCLUSIONS

Study participation in a hospice population of the dying was acceptable. The results will help guide future community study planning.

INTRODUCTION

People with terminal illnesses need timely symptom control and should be able to die in their 'preferred place of care'[1] (usually home[2)]. Dying patients are often too weak to take oral medication. The mainstay in the United Kingdom (UK) is subcutaneous infusions by syringe driver and top-up medication by subcutaneous injection[3]. Family carers can be trained to give injections [4-6]. In the UK, this is less common. Usually, when the terminally ill experience symptoms, a carer calls a community nurse for an injection. It can take hours for nurses to arrive[7]. This is often distressing for patients and families.

In 2015 the Palliative Care and end of life care Priority Setting Partnership published results. It used surveys and a prioritisation workshop with patients, carers and professionals, to identify the top 10 unanswered research questions in palliative/end of life care. Symptom concerns, unscheduled hours, and family support were given priority[8].

There can be disquiet about injections[9,10]. There are alternative preparations given more rapidly and easily – (both fast acting) nasal fentanyl (NF) and buccal midazolam (BM). Research has examined NF for breakthrough pain[11] and BM for seizures[12] but not in the dying. In preparation for a community randomised trial of these administration modes, we assessed study methodology.

METHODS

We started recruitment to a randomised controlled trial from December 2016 but gained approval to recruit an additional third observational arm of BM alone from October 2017. All patients could receive standard as needed medication. Hospice inpatients and carers fitting inclusion criteria were identified as possible participants by the clinical team. If the patient had capacity, the study was discussed with them first and then their carer. Where they lacked capacity, the study was discussed with carer only.

Abbreviated Inclusion Criteria:

- Hospice inpatients
- Terminal cancer; estimated prognosis 1-2 weeks
- Carer/family member willing to give medication AND likely to be at the hospice at least 25% of the time

Study Procedures

Three patient information leaflets AND consent forms were used for: 1) Patients with capacity; 2) Carers; 3) Carers willing to consent on behalf of patients lacking capacity. Potential participants were given information leaflets. After as much time as they wished, they were asked to sign appropriate consent forms. Patients eligble for Groups A and B were randomised via telephone by the sponsoring hospital Research Support Service:

- Group A – NF replaced subcutaneous opioids for pain and BM subcutaneous benzodiazepine for agitation. Group A could receive NF four hourly; up to four times daily on a titration schedule. Once effectively titrated, carers could also administer BM four hourly; up to four times daily.

- Group B – Standard Care – oral, sublingual, or subcutaneous medication (anti-emetics, anti-secretory drugs, benzodiazepines and opioids).
- Patients eligible for Group C – BM replaced subcutaneous benzodiazepine for agitation. Group C could receive BM four hourly; up to four times daily.

Nursing staff could administer trial medication if carers were not present OR not confident.

Carers in Groups A and C received Symptom Management Training Packs about symptom assessment and training on how to use trial drugs:

NF and BM – Group A

BM alone – Group C

Outcome Measures

The following were collected: 1) time to adequate symptom control; 2) need for additional medication; 3) adverse events; 4) time to onset; 5) time from dose to symptom recurrence.

Symptoms were measured by the modified Palliative Care Outcome Scale – symptom module (POS-S)[13] daily. After agreement from Dr Fliss Murtagh (then Reader and Consultant in Palliative Medicine at King's College, London), we removed the question on 'any other symptoms?' and added the anxiety question from the Integrated Palliative care Outcome Scale (IPOS).

Adverse Events

As a study in the terminally ill, it was expected death would be frequent. It was reported to the sponsor, but not considered a serious adverse event if, in the Chief Investigator's opinion, it was a natural conclusion to the illness. Deaths did not

require immediate reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) or Ethics Committee.

Statistical Analysis

For all quantitative outcome measures, the main aim was feasibility of intervention delivery to help design a main trial. Indicative outcomes were underpowered for statistical interpretation.

RESULTS

There were 337 hospice admissions during the study period (320 individuals). 308 did not meet inclusion criteria. Main reasons not terminally ill; not on a high enough background opioid dose; family not present 25% of the time. Of the 29 eligible patients/carers approached, 9 declined. Of the 20 patients enrolled, 3 completed the study, 8 died, and 9 withdrew (family request – 4; adverse event – 2; unable to titrate NF – 2; discharged home - 1). Of 9 in Arm A, 1 died before study drug and 2 withdrew because they could not be titrated on NF (i.e. pain uncontrolled 30 minutes after 800mcg dose). All 9 in Arm B received symptom-relieving medication. Of the 2 in Arm C, 1 did not receive study drug. There were 308 breakthrough episodes requiring medication: Arm A – 165; Arm B – 125; Arm C – 18. There were 85 doses of experimental drug given; 41 post-titration.

Median time from recruitment to death was 7 days; 1 patient lived 119 days. In Arm A, the successful NF dose was 100mcg for 2; 200mcg for 3; 400mcg for 1. Of the 3 given BM (Arms A and C), all responded to 2.5mg. There were missing data for outcome measures but none for dose timing. Results are in Table 1 for the 6 titratable patients in Arm A, 9 Arm B, and 1 in Arm C who received trial medication. Those successfully titrated on study drugs had faster and longer lasting symptom control than standard medication.

Adverse Events

There was one serious adverse event (wrong dose of study drug).

DISCUSSION

It was possible to conduct a feasibility study in a single hospice. When we planned this study, carers administering symptom medications at home were rare. It was thought safer to conduct a feasibility study in a controlled environment. In the years it took to finalise the protocol, secure funding and approvals, a multi-centre, feasibility, community randomised trial has been conducted comparing subcutaneous medication administered by families versus healthcare professionals[14].

It was expected many admissions would be ineligible. Half of the unit's admissions go home. Often the families of those admitted are unable to provide care (or would not be present 25% of the time). Patient/family distress or likely inability to safely administer drug were issues in a few. Families approached often wanted the opportunity to give medication. A future community study would only approach terminal patients wanting to stay at home (perhaps making recruitment easier). Recruitment time was limited by a short expiry date for BM. A substantial amendment was approved for an observational Arm C (BM alone as experimental drug). This led to two patients recruited and while one did not receive study medication, the other did receive symptomatic benefit. There was much missing data. We were wary of burdening patients, families, and busy staff. As the study required caregivers to be present 25% of the time, we anticipated missing data for family assessments. There was much missing nursing assessment data despite research team support including training sessions and 24-hour research team advice.

The drugs were largely well tolerated. Of concern was the wrong dose of NF on three occasions by nursing staff; in one incident, four times the correct dose. We classified this as a serious adverse event. The patient was sleepier but otherwise unharmed. No errors were made by families and these incidents confirm how important training and 24-hour support would be in a potential community study. For a future community study, dose timing, number of doses used, and need for rescue medication from community nurses would be the best outcome measures.

CONCLUSIONS:

We hope to use lessons from this research to plan studies to investigate how best to support patients dying at home and their families. One would expect those in a specialist palliative care unit to have the most complex symptoms and families struggling to cope with home care. A future community study would likely recruit more ‘normal dying’ with easier to treat symptoms and families more able to help. Our study showed that even amongst the most complex illnesses, patients and families are happy to participate.

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CONTRIBUTORS

PP conceived the study. AP and EH made substantial contribution to its design. AP collected most of the data along with BD. RKA was responsible for data analysis. All authors contributed to the analysis and interpretation of the data and critically revised drafts of the paper. They also read and approved the final version of the manuscript. PP is the guarantor.

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Kyowa Kirin provided PecFent supplies free of charge and lock boxes for the trial. Special Products provided Epistatus free of charge. Both companies provided funding to enable the study to be conducted.

COMPETING INTERESTS

All authors have completed the Unified Competing Interests form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding

author). PP and EH have in the past received financial support to attend educational events from Kyowa Kirin.

APPROVALS/ETHICS

The study was approved by Gloucestershire Research Support Service, the Sue Ryder Research Governance Group, the National Research Ethics Service Committee South Central – Berkshire and the MHRA. The clinical trial was registered in EudraCT, the EMEA database for clinical trials (code EUDRACT 2013-005009-30).

TRIAL REGISTRATION

ClinicalTrials.gov Identifier: NCT02009306

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DATA SHARING STATEMENT

Unpublished data are held by Sue Ryder Leckhampton Court Hospice.

TABLE 1: PRIMARY AND SECONDARY OUTCOMES

Outcomes	Median Time: Minutes (Interquartile Range)	
	Experimental Drugs Post-Titration (Arms A, C – 41 Episodes)	**Standard Drugs (Arms A, B, C – 223 Episodes)**
Primary Outcomes		
Time to symptom control from when needed	20 (17.5 – 29.0)	30 (25.0 – 38.0)
Time from medication to onset of symptom control	10 (9.0 – 16.0)	20 (16.0 – 30.0)
Secondary Outcome		
Time from medication to next breakthrough medication	380 (142.5 – 694.0)	275 (152.5 – 537.5)

REFERENCES

1. Sepúlveda C, Marlin A,Yoshida T, *et al.* Palliative Care: The World Health Organization's Global Perspective. *J Pain Symptom Manage* 2002; 24: 91-6.

2.https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthcaresystem/bulletins/nationalsurveyofbereavedpeoplevoices/england2015 (accessed 25 Oct 2018)

3. National Institute for Health and Care Excellence Care of dying adults in the last days of life 2015 https://www.nice.org.uk/guidance/ng31/chapter/Recommendations#pharmacological-interventions (accessed 25 Oct 2018)

4. Working with Unregulated Care Providers College of Nurses of Ontario. 2013. http://www.cno.org/Global/docs/prac/41014_workingucp.pdf (accessed 25 Oct 2018)

5. Anderson B, Kralik D. Palliative care at home: Carers and medication management. *Palliat Support Care* 2008;6:349–56.

6. Healy S, Israel F, Charles MA, *et al.* An educational package that supports laycarers to safely manage breakthrough subcutaneous injections for home-based palliative care patients: Development and evaluation of a service quality improvement. *Palliat Med* 2012;6:562-70.

7. The King's Fund Understanding NHS financial pressures – how are they affecting patient care? 2017 https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/Understanding%20NHS%20financial%20pressures%20-%20full%20report.pdf (accessed 25 Oct 2018)

8. James Lind Alliance Priority Setting Partnerships. Palliative and End of Life Care. 2015 http://www.jla.nihr.ac.uk/priority-setting-partnerships/palliative-and-end-of-life-

care/downloads/Palliative-and-end-of-life-care-PSP-final-report.pdf (accessed 25 Oct 2018)

9. Sheehy-Skeffington B, Mclean S, Bramwell M, *et al.* Caregivers Experiences of Managing Medications for Palliative Care Patients at the End of Life: A Qualitative Study. *Am J Hosp Palliat Me* 2014;31:148-54.

10. Israel F, Reymond L, Slade G, *et al.* Lay caregivers' perspectives on injecting subcutaneous medications at home. Int J Palliat Nurs 2008;14:390-5.

11. Rodriguez D, Urrutia G, Escobar Y, *et al.* Efficacy and Safety of Oral or Nasal Fentanyl for Treatment of Breakthrough Pain in Cancer Patients: A Systematic Review. *J Pain Palliat Care Pharmacother* 2015;29:228-46.

12. Trinka E, Kalviainen R. 25 years of advances in the definition, classification and treatment of status epilepticus. *Seizure* 2017;44:65-73.

13. Collins E, Witt J, Bausewein C, *et al.* A Systematic Review of the Use of the Palliative Care Outcome Scale and the Support Team Assessment Schedule in Palliative Care. *J Pain Symptom Manage* 2015;50:842-53.

14. Wilkinson C, Nelson A, Byrne A, *et al.* CARer-ADministration of as-needed sub-cutaneous medication for breakthrough symptoms in home-based dying patients: a UK study (CARiAD) https://www.journalslibrary.nihr.ac.uk/programmes/hta/151037/#/ (accessed 25 Oct 2018)