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SHORT COMMUNICATION

Analgesic Use and Pain in Robust, Pre-Frail and Frail Older Outpatients with Cancer

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Abstract

Background Pain management can be challenging in frail older people with cancer due to drug–drug interactions and heightened susceptibility to adverse drug events.

Objective To investigate the relationship between analgesic use and pain by frailty status in older outpatients with cancer.

Methods A total of 385 consecutive patients aged 70 years and over who presented to an outpatient oncology clinic between January 2009 and July 2010 completed structured assessments of analgesic use (opioids, paracetamol or non-steroidal anti-inflammatory drugs), pain (10-point visual analogue scale) and clinical factors. Frailty was derived using modified Fried's frailty phenotype. Logistic regression was used to compute adjusted odds ratios (ORs) and 95 % confidence intervals (CIs) for the relationship between analgesic use and pain for each frailty group (robust, pre-frail or frail).

Results For robust outpatients ($n = 101$), there was weak evidence for a 30 % relative increase in the adjusted odds of analgesic use between outpatients who differed by one unit of pain score (95 % CI 0.995−1.71, $p = 0.0532$). For pre-frail outpatients ($n = 190$), there was evidence for a negative quadratic relationship (adjusted OR for the quadratic coefficient: 0.952, 95 % CI 0.910−0.993, $p = 0.0244$). For frail outpatients ($n = 94$), there was an 8 % relative increase in the adjusted odds of analgesic use between outpatients who differed by one unit of pain score, but no statistical evidence for association (95 % CI 0.934−1.26; $p = 0.298$).

Conclusions These findings can be considered for the ongoing development of safe, effective strategies for analgesic use in older outpatients with cancer.

1 Introduction

Pain is highly prevalent in older people and is associated with depression, falls, poor quality of life, sleep disturbance, mobility limitation and decline in physical function [1, 2]. The prevalence of pain doubles from 2 years to 1 month before death [3]. Up to two-thirds of people with advanced cancer report pain [4].

It has been recognized that optimizing pain management in people with cancer requires an individualized approach which seeks to maximize pain relief but minimize the risk of adverse drug events (ADEs) [5, 6]. Frailty is a geriatric syndrome characterized by a decreased homeostatic reserve resulting in an increased susceptibility to ADEs [7].

Analgesics are the most common pain management strategy in older people. However, analgesic prescribing for frail older people is challenging due to increased heterogeneity in drug disposition and response, multimorbidity and changes in body composition [1]. Analgesic selection is complicated by the risk drug–drug and drug–

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disease interactions [8]. Analgesics are frequently implicated in ADEs requiring hospitalization [9]. There is minimal evidence to guide pain management in frail older people. Additionally, since frailty is associated with comorbidity and older age, many frail older people are excluded from participation in clinical trials of analgesics [7].

Cross-sectional studies have identified an association between pain and frailty [2, 10]. To our knowledge, only one previous study has specifically investigated analgesic use and frailty [2]. In this study, more than 65 % of frail older people used analgesics but nearly half wanted their physicians to pay greater attention to pain management. No previous studies have investigated the association between analgesic use, pain and frailty in older people with cancer. This is important because both frailty and analgesic-related ADEs may be exacerbated by cancer and chemotherapy. A patient's first presentation to a geriatric oncology outpatient clinic represents an opportunity to optimize pain management.

The objective of this study was to investigate and characterize the relationship between analgesic use and pain by frailty status in older outpatients with cancer. We expected a higher prevalence of pain among outpatients who were frail, but a less pronounced relationship between analgesic use and pain level due to clinicians being reluctant to prescribe analgesics to people perceived to be at high risk of adverse drug events. This knowledge is important for developing safe and effective strategies for analgesic use in these outpatients.

2 Methods

2.1 Study Population and Data Collection

The study participants and data collection have been described previously [11]. All patients aged 70 years and over who presented at the medical oncology outpatient clinic at the Royal Adelaide Hospital between January 2009 and July 2010 completed a structured data collection instrument.

The instrument captured each participant's age, sex, diagnoses, medications, general pain (10-point visual analogue scale, VAS), instrumental activities of daily living (IADLs [12]), Karnofsky Performance Scale (KPS [13]) physical function (SF-36 [14]), self-reported weight loss over the past 6 months, exhaustion [15, 16] and distress (via a 10-point VAS [17]). The instrument was completed by the outpatient with or without involvement from a family member, and any sections that were incomplete were completed with a nurse at their first visit to the clinic.

Self-reported medication use was verified at the first visit by a nurse with access to each outpatient's medical records, and any medications that were not self-reported were recorded. Data about prescription, non-prescription and complementary and alternative medications (CAMs) were collected separately to ensure a full history was obtained. The validity of the medication lists was estimated by comparing a sample of 30 medication lists to those obtained by clinical pharmacist interviews. There was a greater than 70 % concordance overall, with approximately 80 % concordance for prescription medications [18]. This level of concordance is comparable to medication histories routinely used in hospital wards [19].

2.2 Measures and Definitions

Medications were coded using the Anatomical Therapeutic Chemical (ATC) Codes [20]. Analgesics were defined as opioids (buprenorphine, codeine + paracetamol, dextropropoxyphene, fentanyl, methadone, morphine, oxycodone and tramadol), paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs; celecoxib, diclofenac, ibuprofen, ibuprofen + codeine, indomethacin, meloxicam and naproxen). Analgesic use was defined as use of one or more of these medications.

Frailty was defined using a modified version of Fried's frailty phenotype [15, 21, 22] which considered five criteria: dependence in at least one IADL, weight loss of >5 % over the past 6 months, an exhaustion score of at least three, KPS <70 % and dependence in at least one SF-36 physical function domain. Outpatients were classed as robust if they had none of the criteria, pre-frail if they had one or two of the criteria and frail if they had ≥ 3 of the criteria.

2.3 Statistical Analysis

Demographic and clinical characteristics were summarized numerically and graphically by frailty status (robust, pre-frail or frail). Logistic regression was used to compute unadjusted and adjusted odds ratios (ORs) and 95 % confidence intervals (95 % CIs) for the relationship between analgesic use and pain score for each frailty group separately. The analyses were adjusted for age, Charlson's Comorbidity Index (CCI) and sex. The analyses were performed in the R statistical package [23]. Results were interpreted as suggested by Sterne et al. [24].

2.4 Ethical Considerations

The study was approved by the Royal Adelaide Hospital Human Research Ethics Committee, the University of South Australia Human Research Ethics Committee and the Monash University Human Research Ethics committee [11].

3 Results

Of 413 consecutive outpatients, 385 completed the data collection instrument in full. Robust, pre-frail and frail outpatients had a median age of 77, 75 and 78 years, respectively; 65, 54 and 62 % being male. Robust, pre-frail and frail outpatients used a median of four, five and seven medications, respectively. All frailty groups had a median CCI of 1.

Outpatients who were frail had higher pain scores (Fig. 1; medians of 1, 2 and 5 for robust, pre-frail and frail outpatients, respectively) and had a higher prevalence of analgesic use (corresponding percentages of 21, 34 and 53 %; Fig. 1). Analgesic users who were frail used more medications (medians of six, eight and nine for robust, pre-frail and frail outpatients who used analgesics, respectively). Of the analgesic users in the robust group ($n = 21$), five (24 %) used an opioid, 14 (67 %) used paracetamol, five (24 %) used an NSAID and three (14 %) used more than one analgesic. Of the analgesic users in the pre-frail group ($n = 65$), 32 (49 %) used an opioid (most commonly oxycodone; $n = 15$), 44 (68 %) used paracetamol, 18 (28 %) used an NSAID (most commonly celecoxib; $n = 15$) and 30 (46 %) used more than one analgesic. Of the analgesic users in the frail group ($n = 50$), 29 (58 %) used an opioid (most commonly oxycodone; $n = 19$), 31 (62 %) used paracetamol, four (8 %) used an NSAID and 24 (48 %) used more than one analgesic.

Figure 2 displays the unadjusted relationship between analgesic use and pain by frailty status. For robust outpatients, there was weak evidence for a 30 % relative increase in the odds of analgesic use between outpatients who differed by one unit of pain score after adjusting for age, CCI and sex (95 % CI for the OR 0.995−1.71, $p = 0.0532$). For pre-frail outpatients, there was evidence for a negative quadratic (i.e. concave) relationship between the log odds of analgesic use and pain (adjusted OR for the quadratic coefficient: 0.952, 95 % CI 0.910−0.993, $p = 0.0244$). For frail outpatients, there was an 8 % relative increase in the adjusted odds of analgesic use between outpatients who differed by one unit of pain score, but no statistical evidence for association (95 % CI 0.934−1.26, $p = 0.298$).

4 Discussion

This was the first study to investigate the association between analgesic use and pain in older outpatients with cancer. The main findings were that analgesic use increased linearly with pain in robust and frail outpatients, but there was a concave relationship between analgesic use and pain in pre-frail outpatients. There was a graded association between pain, analgesic and overall medication according to frailty status. Robust outpatients had a lower prevalence of pain, analgesic and overall medication use than frail outpatients.

The magnitude of the positive linear relationship between analgesic use and pain was most pronounced in the robust group, which may indicate that clinicians feel that the benefits of analgesics in robust older people with cancer outweigh potential risks. For the frail group, this positive linear relationship was less pronounced, with lesser prescribing of analgesics per unit difference of pain. This may reflect clinicians' caution with prescribing analgesics in this vulnerable group of this cohort. The higher prevalence of pain in pre-frail and frail outpatients suggests possible underuse of pharmacological and non-pharmacological treatment approaches. This is consistent with previous research demonstrating that age-related physiological

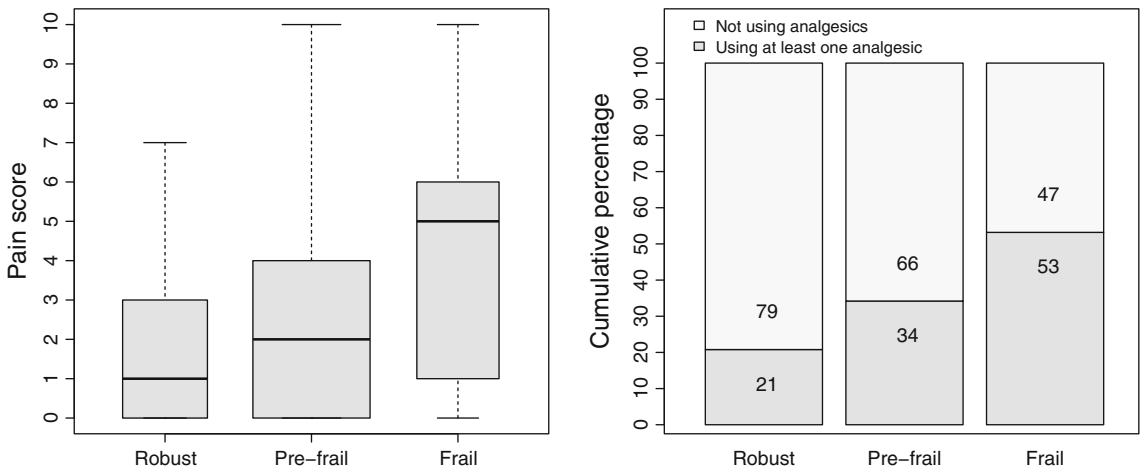

Fig. 1 Distributions of pain score and analgesic use by frailty status

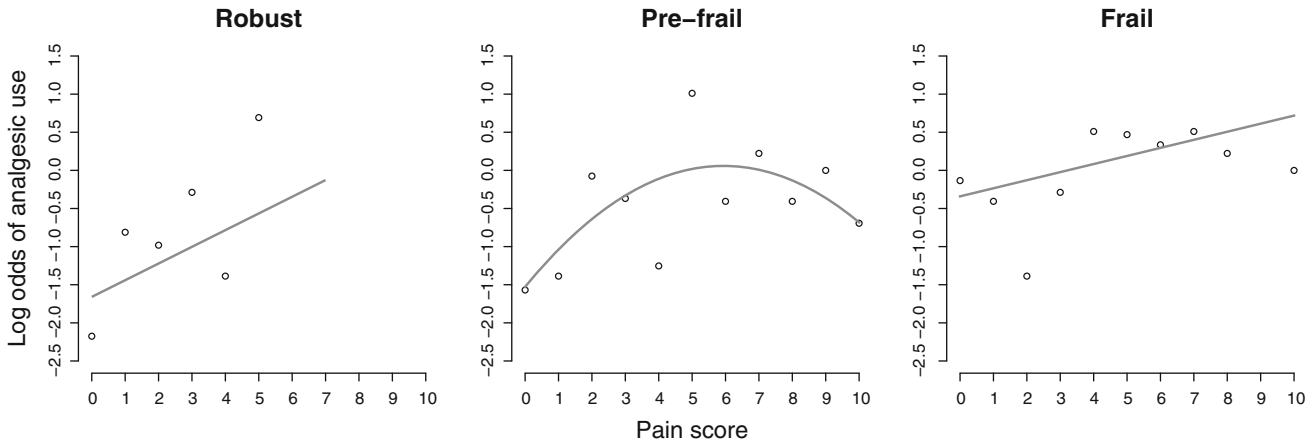

Fig. 2 Unadjusted associations between analgesic use and pain score by frailty status

changes, polypharmacy and multi-morbidity are potential barriers to effective pain management [25].

Interestingly, the relationship between analgesic use and pain was concave in the pre-frail group. This may represent hesitation in prescribing analgesics to pre-frail older people with cancer experiencing higher levels of pain. These people may have been susceptible to ADEs, drug–drug interactions and/or progression to frailty. Recognizing and treating pain in pre-frail outpatients is important because pain is associated with depression and can negatively impact quality of life and function [26, 27].

Our study also demonstrated differences in the types of analgesics prescribed according to frailty status. People who were robust were more likely to receive NSAIDs ($n = 5$, 24 %) and less likely to receive opiates ($n = 5$, 24 %) when compared to people who were frail (NSAIDs $n = 4$, 8 % and opiates $n = 29$, 58 %). This may reflect prescribers' desire to avoid ADEs and drug–drug interactions in frail people. Additionally, people who were pre-frail had high levels of both NSAIDs ($n = 18$, 28 %) and opiates ($n = 32$, 49 %), reflecting the complexity of treating pain in this group.

4.1 Strengths and Limitations

Demographic, clinical and medication data were collected using a structured data collection instrument and verified at the initial consultation. The measure of pain used in this study is well established [28] and has been shown to be valid, reliable and appropriate for overall pain in a clinical setting [29]. However, since it was a measure of general pain, we could not assess the prevalence of particular types of pain, such as neuropathic or musculoskeletal. Nevertheless, this non-discriminatory measure of pain was consistent with our non-discriminatory definition of analgesic use. The study did not assess the stage of cancer. It is possible that outpatients with more advanced cancer may be more likely to be frail, and may experience more pain, regardless of the analgesic used. We did not distinguish between regular and as-needed use of analgesics, or investigate the use of adjuvant therapies or non-pharmacological treatments. The study was conducted in a single outpatient oncology clinic, hence the results may not be generalizable to other geriatric oncology cohorts. As this study was cross-sectional, it was not possible to describe individual outpatient trajectories of analgesic use over time, and how these trajectories related to pain and frailty transitions. Thus longitudinal studies are warranted.

5 Conclusions

In this cohort of older people recently diagnosed with cancer, analgesic use increased linearly with pain in robust and frail outpatients, and there was evidence for a concave relationship between analgesic use and pain in pre-frail outpatients. Our findings suggest additional strategies are needed to optimize analgesic use in older outpatients with cancer, particularly in pre-frail outpatients experiencing high levels of pain. Future research should investigate the role of analgesics as part of a comprehensive and high quality approach to pain management in these outpatients.

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