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ORIGINAL ARTICLE

An international, open-label, randomised trial comparing a two-step approach versus the standard three-step approach of the WHO analgesic ladder in patients with cancer

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Background: Worldwide, cancer pain management follows the World Health Organization (WHO) three-step analgesic ladder. Using weak opioids (e.g. codeine) at step 2 is debatable with low-dose strong opioids being potentially better, particularly in low- and middle-income countries where weak opioids are expensive. We wanted to assess the efficiency, safety and cost of omitting step 2 of the WHO ladder.

Patients and methods: We carried out an international, open-label, randomised (1 : 1) parallel group trial. Eligible patients had cancer, pain $\geq$4/10 on a 0-10 numerical rating scale, required at least step 1 (paracetamol) of the WHO ladder and were randomised to the control arm (weak opioid, step 2 of the WHO ladder) or the experimental arm (strong opioid, step 3). Primary outcome was time to stable pain control (3 consecutive days with pain $\leq$3). Secondary outcomes included distress, opioid-related side-effects and costs. The primary outcome analysis was by intention to treat and the follow-up was for 20 days.

Results: One hundred and fifty-three patients were randomised (76 control, 77 experimental). There was no statistically significant difference in time to stable pain control between the arms, $P = 0.667$ (log-rank test). The adjusted hazard ratio for the control arm was 1.03 (95% confidence interval 0.72-1.49). In the control arm, 38 patients (53%) needed to change to a strong opioid due to ineffective analgesia. The median time to change was day 6 (interquartile range 4-11). Compared to the control arm, patients in the experimental arm had less nausea ($P = 0.009$) and costs were less.

Conclusion: This trial provides some evidence that the two-step approach is an alternative option for cancer pain management.

Key words: pain, cancer, opioids, trial

INTRODUCTION

Pain is the most common and most feared symptom in patients with cancer.[1,2] To address this, almost four decades ago, the World Health Organization (WHO) published the analgesic ladder for treatment of cancer pain and this remains the main teaching tool in palliative care worldwide (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.08.083).[3,4] These guidelines recommend using non-opioids [nonsteroidal anti-inflammatory drugs and paracetamol (acetaminophen)] for mild pain, which constitutes step 1. The second step of the ladder is to add an opioid for mild-to-moderate pain (codeine, tramadol). The third step constitutes an opioid for moderate-to-severe pain (morphine) which is titrated to pain relief or to occurrence of dose-limiting adverse events (AEs). Validation studies have shown that the WHO analgesic ladder can provide pain control in up to 80% of patients.[3,5-8]

Since its inception, there has been a call for randomised controlled trials (RCTs) to explore whether it would be beneficial for patients to move directly from step 1 (non-opioids) to step 3 (strong opioid), omitting step 2 (weak

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opioid).[9] A study of 900 patients showed that >50% of patients needed to switch from step 2 to step 3 within 2 weeks, due to lack of pain control.[10] Small studies have supported the use of omitting step 2 in opioid-naïve patients.[11,12]

Two RCTs published in 2004 and 2005, respectively, demonstrated improved pain control in patients with cancer when moving directly to a strong opioid rather than via a weak opioid used in step 2.[13,14] Although these trial observations are encouraging, it is still not known whether omitting step 2 (weak opioid) of the WHO ladder results in more effective and, importantly, more efficient (quicker) pain control but without an excess of opioid-related side-effects. Also, it is not known which approach, if any, is more cost efficient.

Our hypothesis was that moving to a strong opioid directly from non-opioid analgesia and omitting the weak opioid step achieved quicker pain control and without additional side-effects. Therefore, the primary aim of the present trial was to assess this in an international RCT.

PATIENTS AND METHODS

Study design and participants

We carried out a randomised, open, parallel group trial (clinical trial number: NCT01493635) at cancer centres and palliative care units in the UK (Edinburgh Cancer Centre, Beatson West of Scotland Cancer Centre, Velindre Cancer Centre, Sherwood Forest Hospitals, Walsall Healthcare NHS Trust), Israel (Western Galilee Hospital), Mexico (Instituto Nacional de Cancerología, Tlalpan) and Uganda (Mulago, Uganda). The study was widely publicised via the European Palliative Care Research Centre (PRC) with an open invitation for centres in any country to take part. The choice of countries/centres represents those who expressed an interest to take part and had the necessary infrastructure and governance in place to conduct the study. Eligible patients had cancer, were ≥18 years of age and had average pain rated at ≥4 on a numerical rating scale (NRS) from 0 to 10. Patients could be on simple analgesia (step 1 of the WHO analgesic ladder, e.g. paracetamol) or may not have been taking any analgesia, but due to pain required step 2 of the WHO (weak opioid, e.g. codeine). Patients were excluded for the following reasons: unable to comply with trial procedures; had received any regular opioid (preceding 2 weeks) or immediate-release opioid (>2 doses in the previous 24 h); had received radiotherapy (XRT) in the previous 6 weeks or were planned to receive XRT during the trial period; had pain due to surgery in the preceding 4 weeks; had a life expectancy <2 months; were planned to have or had a nerve block during the trial; or had psychotic disorders or cognitive impairment.

The trial was conducted as per Good Clinical Practice guidelines and had necessary regulatory and ethical approvals in all countries in which it was conducted. All patients provided written informed consent.

Randomisation and masking

Patients were randomised centrally using a web-based portal (www.tvttrial.org), following registration. This was supported by the Edinburgh Clinical Trials Unit, Edinburgh, UK. Minimisation incorporated a random component and stratification for the following factors: centre, sex, age (18-69; 70+ years), on current systemic anticancer therapy treatment (yes/no) and baseline average pain score (4-5; 6-7; 8-10). Allocation was done on a 1 : 1 basis to either the control arm, started on step 2 (weak opioid) and if needed changed to step 3 (strong opioid), or to the experimental arm, started on step 3 (strong opioid) (see Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.08.083).

Procedures

In the control arm, patients received a weak opioid, either tramadol (maximum dose 100 mg qds) or codeine (maximum dose 60 mg qds), the choice of which, along with the starting dose, was made by the local investigator. Breakthrough analgesics (either weak or strong opioids) were not permitted in the control arm as patients were already on a maximum recommended dose of a weak opioid. The maximum doses and exclusion of breakthrough use were in line with WHO guidance.[15] Pain relief was defined as not achieved if average pain score remained ≥4 and, in the opinion of the investigator after discussion with the patient, meaningful pain improvement had not been achieved despite the maximum dose of codeine or tramadol.

The experimental arm was a two-step approach to analgesia, where patients started a strong opioid immediately. The opioid was morphine or oxycodone, the choice of which, along with the initial dose and titration, was determined by the local investigator.

There were no specific dose restrictions of strong opioid, either the starting dose or the maximum dose, in either arm of the trial as per WHO guidelines on the management of cancer pain in adults.[15] Patients in the control arm could use only one opioid for mild-to-moderate pain during the trial. Patients in either arm who were taking a strong opioid could change from morphine to oxycodone or vice versa during the trial if the investigator was of the opinion that this was clinically appropriate.

Patients were allowed to take other analgesics (adjuvant and non-opioid analgesics) during the course of the trial; however, changes in the dose of pre-trial adjuvant or non-opioid analgesics were not permitted. Commencing adjuvant analgesics or non-opioid analgesics during the trial was not allowed.

Assessments

The following were assessed at baseline (day 1, pre-randomisation): demographics; cancer type; pain assessed on a 0-10 NRS; Brief Pain Inventory (BPI)[16]; the National Comprehensive Cancer Network (NCCN) Distress Thermometer[17]; opioid toxicity and side-effects questionnaire; EuroQol five-dimensional (EQ-5D-5L) questionnaire.[18]

During the 20 days' trial period, every day patients recorded average pain, worst pain and analgesic use in a diary using an NRS and structured analgesic use record. Patients were phoned daily by trial staff who were an extended part of a supportive or palliative care team and were unblinded as to the trial arm. Trial staff had palliative care training but were not specialists in palliative care. The trial staff worked with the patient to facilitate completion of the patient diaries and assessed the use of analgesic and non-analgesic medication, as well as opioid toxicity and side-effects (nausea, vomiting, constipation, drowsiness, confusion, disorientation, hallucinations, shadows at the corner of the eyes, vivid dreams, jerks). In designing this trial, a key consideration was to record any opioid-related AEs. To achieve this, we used an opioid toxicity and side-effect questionnaire where we included all potential side-effects. We acknowledge that some of these (e.g. vivid dreams and pseudo-hallucinations) may not be considered as typical side-effects but have been reported as heralding the more major opioid side-effects such as hallucinations and confusion.[19] On day 10 and day 20, the BPI, NCCN Distress Thermometer and EQ-5D-5L questionnaire were completed.

Outcomes

The primary outcome was time to achieving stable pain control, where stable pain control was defined as the first day of 3 consecutive days with average pain score $\leq$3 on an NRS 0-10. An NRS $>$3 correlates with moderate (4-6) or severe (7-10) pain from several studies and systematic reviews.[20] The standard operating procedure (SOP) was clear that there should be no forced titration, but titration should follow usual best clinical practice and be agreed by the patient. If stable pain control was not achieved during the period of data collection, then the censoring date was taken as the last day on which there was evidence of pain control not being achieved.

Secondary outcome measures were mean of daily average pain scores, mean of daily worst pain scores, percentage of days with average pain score $\geq$6, percentage days with worst pain score $\geq$6, pain intensity, pain relief and pain interference scores at day 10 and 20 and patient distress score at day 10 and 20.

Side-effects were also measured. Primary measures were a symptom score of 1 or more reported during the trial for each of 10 symptoms. Secondary measures were the frequency of reporting a symptom score of 1 or more for each of the 10 symptoms, the worst daily score for each of the symptoms and the number of days in which a symptom was present.

Statistics

The original target sample size was 400 participants (200 in each arm) and this was calculated using a standard approach with 90% power (type I error of 5%) to detect an increase from 60% to 75% in the proportion of patients who achieve stable pain control by 20 days using a log-rank test (two-sided) to compare the time to stable pain control between the experimental and control arms. However, at the end of our target recruitment period of 3 years, the recruitment rate was inadequate ($\sim$50 patients per year worldwide) and it would have taken $\sim$5 more years to complete the trial (8 years in total). Therefore, following statistical and trial steering committee guidance, it was agreed to close the trial at this point (153 patients) and undertake analysis. All patients randomised were included in the analysis using an intention-to-treat approach.

Kaplan–Meier estimates of the cumulative proportion of patients who achieved stable pain control during the trial were plotted for each arm. The time to stable pain control in the two arms was compared using the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) for the intervention arm versus the control arm were estimated using a Cox proportional hazards model with region (Europe/Mexico/Uganda), sex (M/F), age ($<$70/70+ years), whether the patients were on current chemotherapy treatment (yes/no) and baseline average pain score (4-5/6-7/8-10) as covariates.

The mean of the daily average pain scores for each patient, mean of the daily worst pain scores for each patient, percentage of days with average pain score $\geq$6 and percentage of days with worst pain score $\geq$6 were analysed using analysis of covariance, with region, sex, age, currently receiving chemotherapy and baseline pain score as covariates. The difference in means and 95% CI, for the experimental arm versus the control arm, was estimated from this model.

The proportion of patients in the two arms who reported each of the 10 symptoms of opioid-related side-effects and toxicity during the trial was analysed using logistic regression, with region, sex, age, whether the patient was on current chemotherapy treatment and baseline score for the side-effect as covariates. The odds ratios and 95% CI for the two-step approach versus the three-step approach were estimated from this model. As the trial was underpowered, these should be regarded as explorative. The number of AEs and serious adverse events (SAEs) are presented descriptively.

Health economic analysis

The aim of the health economic analysis (within trial analysis) was to calculate the incremental cost-effectiveness ratio [ICER, difference in costs per additional quality-adjusted life year (QALY)] of the control arm versus the experimental arm. Costs are limited to medication costs, taken as the sum of opioid costs including breakthrough opioids and concomitant medication. For cost assignment of the UK costs, the UK Department of Health electronic Medicines Information Tool (eMIT) for generic drug costs[21] and the British National Formulary[22] for on-patient costs were used. For the Mexican costs, data sources were Incan[23] and Farmacos Especializados.129117Grupo Fármacos Especializados2016.[24] Costs in Uganda were provided by the local research team and pharmacist.

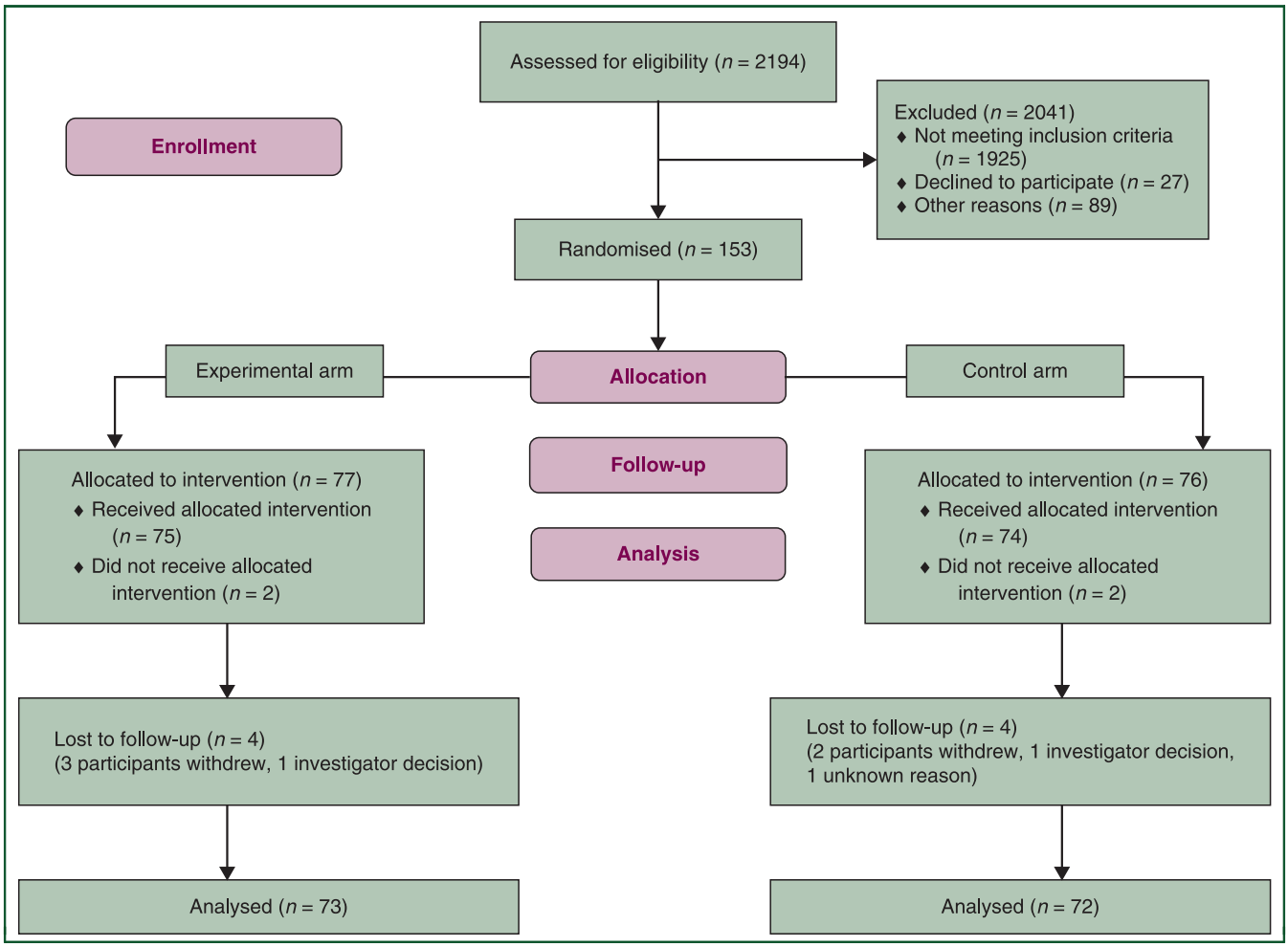

Figure 1. **Trial profile.**

The utility weights were derived from the EQ-5D-5L using the crosswalk method[25] to assign a tariff representative of EQ-5D-3L UK value sets, measured on days 0, 10 and 20, with intervening days imputed by linear interpolation. Missing resource use data were assumed to take zero cost. Patients who died were subsequently assigned a utility value of zero. Missing EQ-5D-5L values were imputed by linear interpolation. Crosswalk data from EQ-5D-5L to EQ-5D-3L are only available for certain countries including the UK but not available for Mexico and Uganda. Therefore, the analysis was restricted due to the availability of data. The final analysis consisted of a cost-utility analysis for the UK, including a sensitivity analysis and a cost analysis for Mexico and Uganda. Uncertainty was explored by bootstrap (case resampling) of the data with 1000 replications. The probability that the two-step ladder was cost-effective compared to the three-step ladder at the current National Institute for Health and Clinical Excellence (NICE) threshold of £20 000 per QALY was calculated.

Role of the funding source

We are grateful to The Edinburgh Doreen McGuire Endowment Fund and an unrestricted educational grant from Mundipharma which contributed to research nurse costs. The study protocol was developed in collaboration with the PRC, Norway. No funding source had any input into the design or conduct of this investigator-led study. Participating sites contributed to costs by using their research staff for recruiting patients and collecting data.

RESULTS

Between 3 January 2013 and 31 March 2016, 153 patients consented to the trial (Figure 1). Of these, 76 were randomised to the control arm and 77 to the experimental arm; however, 8 were lost to follow-up after randomisation (4 in each arm), leaving a total analysed of 145 (73 in the experimental arm and 72 in the control arm). Two patients were randomised (who did not meet the eligibility criteria); however, they were included in the analysis.[26]

Baseline characteristics are presented in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.08.083, and the groups were well balanced with respect to age, gender, region and pain scores. The median age was 61 years [interquartile range (IQR) 50-72 years]. The most common cancer types were gynaecological (42/153, 27%), gastrointestinal (28/153, 18%) and head and neck (23/153, 15%), and 77 (50%) patients had metastatic disease.

Figure 2 represents the primary outcome analysis. No significant difference was demonstrated for time to stable pain control between the experimental and control arms, $P = 0.667$ (log-rank test). Adjusting for age, sex, region, whether the patient was on chemotherapy and baseline average pain score (compared to the experimental arm), for the control arm the HR was 1.03 (95% CI 0.72-1.49). In the control arm ($n = 72$), patients received the following as their first weak opioid: codeine 23 (32%) and tramadol 45 (63%), note 1 patient received morphine and 1 patient received oxycodone in error. In the experimental arm, 50 (68%) received morphine and 21 (29%) received oxycodone as their first strong opioid, note 1 patient received codeine and 1 patient received tramadol in error.

Table 1 details the secondary outcome analysis. There were no statistically significant differences between the control and experimental arms in adjusted means (standard deviation) of daily average pain scores. Assessing the BPI scores, there was a significant difference in global distress at day 20 between the control and experimental arms [2.68 (2.72) versus 1.69 (2.05); $P = 0.0270$]. Of patients in the control arm, 38 (53%) needed to change to a strong opioid. The median (IQR) day that this was done was day 6 (4-11).

Figure 3 shows the Kaplan–Meier plot of time to stable pain control for patients in the control arm, categorised as to whether they needed to change to a strong opioid or not. The median time to stable pain control was 7 (4-17) days in those patients who needed to change to a strong opioid versus 3 (2-5) days in those who did not need to move to a strong opioid.

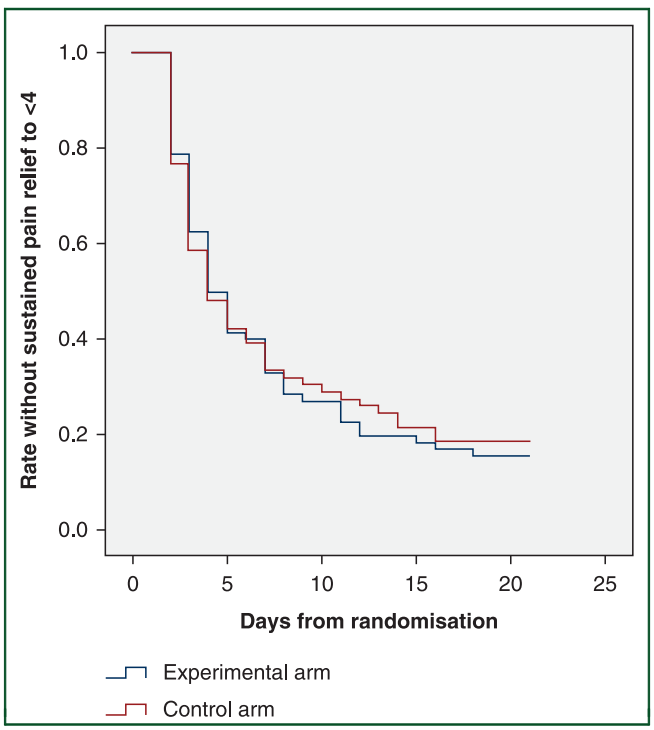

Figure 2. Kaplan–Meier plot of time to stable pain control. $P = 0.667$ (log rank, between arms). Adjusting for age, sex, region, whether the patient was on chemotherapy and baseline average pain score (compared to the experimental arm), for the control arm the hazard ratio was 1.03 (95% confidence interval 0.72-1.49).

Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.08.083, details opioid-related side-effects between trial arms. Compared to patients in the control arm, patients in the experimental arm had a 2.93 times lower odds of experiencing nausea (95% CI 1.31-6.58; $P = 0{\cdot}009$). Antiemetics were prescribed to 10 (13%) patients in the experimental arm and 13 (17%) patients in the control arm, during the trial. Laxatives were prescribed to 22 (29%) patients in the experimental arm and 25 (33%) patients in the control arm, during the trial. The median (IQR) of the morphine equivalent daily dose at day 10 was 30 mg (20-45 mg) in the experimental arm and 40 mg (20-40 mg) in the control arm. The median (IQR) of the morphine equivalent daily dose at day 20 was 30 mg (20-40 mg) in the experimental arm and 40 mg (26-45 mg) in the control arm.

Supplementary Figure S2A-D, available at https://doi.org/10.1016/j.annonc.2022.08.083, shows the number of days individual patients experienced nausea, vomiting, disorientation and shadows per trial arm. The total number of days patients experienced nausea and vomiting was 270 days (experimental) versus 390 days (control) and 105 days (experimental) versus 195 days (control), respectively.

There were 93 AEs reported [51 control (19 patients), 42 experimental (17 patients)] and 8 SAEs [5 control (5 patients), 3 experimental (3 patients)]. Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.08.083, shows SAEs. There were five in the experimental arm (unrelated) and four in the control arm (three possibly related).

Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.08.083, details the health economic analysis. In the UK population, total costs were £49.72 and £57.83 for the experimental and the control arms, respectively. The UK cost of opioids was less expensive in the control arm, but there was a higher cost for concomitant medication, making the experimental arm less expensive overall. The difference is larger in Mexico due to the higher cost of weak opioids: the mean 20-day drug cost was US$51.74 versus US$182.54. Costs in Uganda were 3.06 UGX and 18.91 UGX for the experimental and control arms (data not shown), respectively, again due to higher costs of weak opioids.

Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.08.083, details analysis of QALYs. The experimental arm produced higher QALYs in the UK resulting in 12.44 (95% CI) out of 20 possible quality-adjusted life days compared with 10.87 (95% CI) days with the control arm. The ICER for UK patients for the experimental arm dominates the control arm at £−5.17 per QALY. This results from having an intervention (experimental arm) which is more effective (1.57 quality-adjusted life days within a timeframe of 20 days) and less costly (£8.11 less per patient) than current practice (control arm). The probability that the two-step ladder is cost-effective in the UK is >70% taking into account the NICE cost-effectiveness threshold of £20 000 per QALY.

Table 1. Pain characteristics over 20 days per study arm ($n = 145$)

	Control arm		Experimental arm		*P* value[a]	Difference in mean scores (95% CI)
	Mean	SD	Mean	SD		
Average pain	2.57	1.53	2.48	1.61	0.639	0.09 (−0.61 to 0.43)
Worst pain	4.14	1.90	3.75	1.83	0.220	0.39 (−1.01 to 0.22)
Percentage of days with average pain >6	10.7	19.7	10.5	19.9	0.889	0.29 (−6.73 to 6.26)
Percentage of days with worst pain >6	30.0	33.3	24.0	26.3	0.251	6.07 (−15.92 to 3.78)
Brief pain inventory[b]						
Pain intensity D10	2.28	1.39	2.39	1.75	0.700	0.12 (−0.47 to 0.71)
Pain relief D10	71.0	22.93	69.7	24.9	0.668	−1.8 (−10.2 to 6.5)
Pain interference D10	2.49	2.38	2.36	2.22	0.802	0.09 (−0.81 to 0.62)
Global distress score D10	3.56	2.47	3.30	2.45	0.729	0.15 (−0.99 to 0.69)
Pain intensity D20	1.38	1.14	1.38	1.40	0.861	0.04 (−0.50 to 0.42)
Pain relief D20	82.0	20.3	85.0	18.5	0.257	3.9 (−2.8 to 10.5)
Pain interference D20	1.51	1.88	1.46	1.95	0.876	0.05 (0.69 to 0.58)
Global distress score D20	2.68	2.72	1.69	2.05	0.027	0.93 (−1.75 to −0.12)

This table describes pain scores over days 2-20 and therefore includes only patients with follow-up data ($n = 145$).
CI, confidence interval; SD, standard deviation.
[a]Two-sample *t*-test adjusted for age, sex, region, on chemotherapy treatment and baseline average pain.
[b]D10 and D20 correspond to days 10 and 20, respectively.

DISCUSSION

Although underpowered, our RCT demonstrated several findings. Firstly, the experimental arm (direct to a strong opioid) did not result in faster pain relief than the control arm (weak opioid step). However, it is notable that in the control arm more than half of the patients required to switch from a weak to a strong opioid to achieve stable pain control. Secondly, and importantly, moving from a non-opioid to a strong opioid in this study was safe; in fact, there were fewer opioid-related side-effects compared to the control arm. Thirdly, the cost of the experimental arm was less than that of the control arm, the latter being standard care. In countries where strong opioids are limited, such as in low- and middle-income countries, weak opioids are usually very expensive and this study helps to make a case for increased access to strong opioids globally.

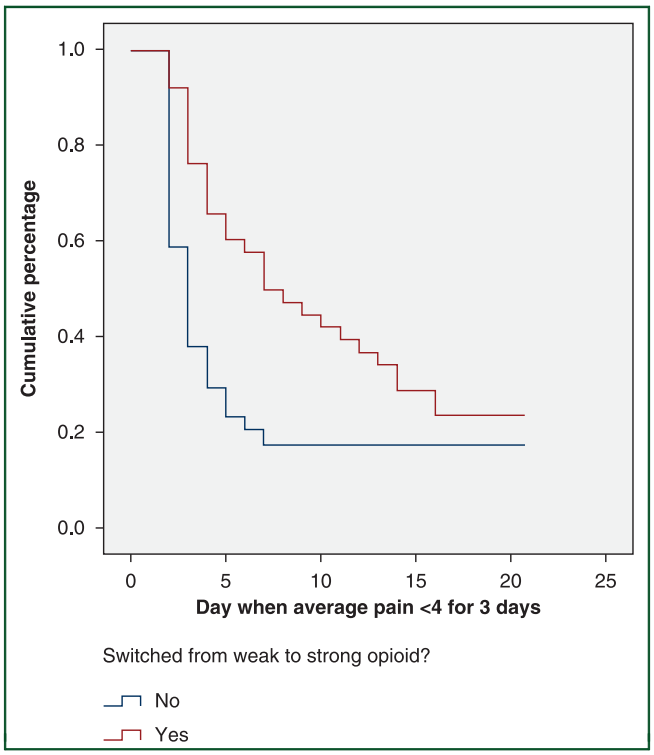

Figure 3. Kaplan–Meier plot of time to stable pain for patients in the control arm.

It is important to acknowledge two important aspects of this trial which may have influenced the findings. Firstly, those patients who have inadequate pain relief from a weak opioid are likely to wait longer to be switched to a strong opioid than was the case in this study where patients had a daily pain assessment. This would rarely happen in clinical practice. Secondly, the costs do not include the costs to the patient, and to the health care system, of an extra consultation and prescription for the switch to a strong opioid in those who fail on a weak opioid. These are notable observations when interpreting the study in relation to clinical practice.

A key design strength of our trial is that we defined the primary outcome as the time to when pain control was achieved (first day of 3 consecutive days with average pain score ≤ 3 on an NRS 0-10) which is crucially related to improved function. Other studies took the more limited primary outcome of a 2-point drop on a 0-10 pain scale.

A recognised barrier to strong opioid prescribing is a fear of opioid-related side-effects. Therefore, we sought to assess this in detail and to our knowledge this provides the most extensive and accurate reflection of opioid-related side-effects when introducing opioids to date. By using direct nurse discussion with the patient about the daily assessments of side-effects, we have confidence in the results and concluded that starting strong opioid analgesia from a non-opioid certainly has no more and potentially fewer side-effects than starting weak opioid analgesia. The inefficiency of the weak opioid step observed in the present study (>50% of patients found this ineffective) is notable due to the practicalities in some countries of switching to a strong opioid in the community.

To our knowledge, this is the first assessment of the WHO analgesic ladder which has undertaken a cost comparison. From a UK perspective where the three-step analgesic ladder is slightly more expensive than the two-step, the ICER was £−5.17 indicating that the two-step ladder is less costly and more effective. In the Mexican and Ugandan settings, the difference in costs in favour of the two-step ladder was even greater. This suggests that especially in countries where the costs of weak opioids are high, a switch to a two-step ladder is cost saving. The lack of utility weights precludes making a statement regarding cost-effectiveness.

Limitations

The trial has several limitations. Recruitment was inadequate and the trial closed to recruitment after 153 patients, meaning that the trial was underpowered. As trial staff who conducted daily assessments were aware of the trial arm, this may have introduced reporting bias. The choice of strong opioids in the study was informed by those most commonly used when starting an opioid for moderate-to-severe pain worldwide. The study was aimed at providing evidence for generalists/non-specialist palliative care clinicians who prescribe opioids for cancer-related pain. The standard operating practice was that nothing should happen to a patient within the study which the clinician would not normally do in their clinical practice, including a preference for other opioids in cases such as renal impairment or certain pains. We accept that in patients with a degree of renal impairment some opioids (e.g. fentanyl) may be preferable. Assessing multiple opioids was not within the remit of the present study; therefore, application of our findings to patients with renal impairment should be done with caution. The same rationale applies to preference for certain opioids in specific pains. We would also highlight that management of opioid-related side-effects was not standardised across countries, but followed local guidelines which could have resulted in a difference in outcomes between sites. However, we did not note any difference in side-effects between study sites. There are few studies of opioid-related side-effects which assess these so regularly and in such detail. The attention to detail in this study is undoubtedly associated with identifying more side-effects. We would also highlight that management of opioid-related side-effects was based on local guidelines in each country as these were assessed by the study team as very similar in content, but allowed the use of locally available drugs. We did provide an SOP about detail to assessment and management of side-effects. We did not note any difference in side-effects between study sites.

In addition, the trial was designed to achieve adequate statistical power for the study primary outcomes rather than the economic outcomes (cost and QALYs). Therefore, the main limitation of the health economic analysis is that the differences for the economic outcomes between two-step and three-step ladders did not achieve statistical significance possibly due to low statistical power. This is reflected in the bootstrap analysis but caution should be used when interpreting the magnitude of the reported differences in costs and QALYs.

Conclusion

In summary, our findings provide some evidence that a two-step approach is an alternative option for cancer pain management and may be less expensive than a three-step approach. Currently, international guidelines give weak recommendations for bypassing step 2 of the analgesic ladder and going straight from non-opioids to low doses of an opioid for moderate-to-severe pain.[27,28] Limitations with existing studies have prevented the level of evidence from being rated higher. The present RCT may help inform the prescriber who wishes to omit step 2 of the WHO ladder.

FUNDING

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DISCLOSURE

MF has received educational grants from Pfizer. BJAL has done consultancy for Artelo and XBiotech. All other authors have declared no conflicts of interest.

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This study was initially conceived by late Prof. Geoffrey Hanks. MF, AC, SK and BJAL designed the research (project conception and study oversight); MF led the research. BJAL and GDM analysed the data and carried out the statistical analysis. KD and PSH designed and conducted the cost analysis. All authors contributed to data collection and contributed to the interpretation of results and writing of the manuscript. MF had the primary responsibility for the final content. All authors had final approval of the manuscript.

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