BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003061
Article Type:	Research
Date Submitted by the Author:	15-Apr-2013
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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Medical management
Keywords:	chronic pain, drug delivery systems, implantable, morphine, randomised controlled trial, treatment efficacy

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Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain

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Word count: 3,357

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ARTICLE SUMMARY

Article focus

- Recent systematic reviews were unable to find randomised controlled trials evaluating the effectiveness of long-term intrathecal drug delivery systems for the management of chronic non-cancer pain.

- We aimed to investigate if a small decrease in the intrathecal morphine dose leads to an increase in reported pain scores in chronic non-cancer pain patients undertaking long-term intrathecal morphine.

- The randomised controlled trial design would allow to investigate the long-term efficacy of intrathecal morphine delivery.

Key messages

- Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction.

- The findings of this study support the efficacy of intrathecal morphine delivery for the management of chronic non-cancer pain.

Strengths and limitations of this study

- To our knowledge, this is the first randomised controlled trial investigating the efficacy of intrathecal drug delivery systems for the management of chronic non-cancer pain.

- By investigating patients with intrathecal delivery for a minimum of 12 months this study is not confounded by need for dose titration and the non-specific psychological effects of a major intervention.

- Limitations of this study include small sample size and being conducted in a single centre.

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ABSTRACT

Objective

This study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity.

Design

Randomised, double blind, controlled, parallel group trial.

Setting

Department of Pain Management, Russells Hall Hospital, Dudley, United Kingdom.

Participants

Twenty-four non-cancer pain patients implanted with morphine reservoirs were assessed for eligibility.

Interventions

The participants were randomly allocated to one of two parallel groups in which one of the groups had no change in the morphine dose and the other group had a small reduction (20%) in dosage every week during a 10-week follow-up.

Outcome

Primary outcomes were visual analogue scale (VAS) pain score change and withdrawal from study due to lack of efficacy.

Results

Nine of the patients assessed for eligibility declined to participate in the study. Fifteen patients were randomised to control (n=5) or intervention (n=10). Due to worsening of pain, seven patients withdrew from the study prematurely. None knew prior to withdrawal which arm of the study they were in, but all turned out to be in the dose reduction arm. Calculation of drop-out rate between groups indicated a significant statistical difference (p = 0.026). Recruitment ceased at that moment. Statistically significant differences for VAS were observed between baseline and last observation in the group randomised to have dose reduction but not in the control group (p = 0.188). VAS was significantly lower at baseline (Mdn = 49.5) than at last observation (Mdn = 77.5) for the reduction group, Z = -2.805, p = 0.002, r = -0.627.

Conclusion

This double blind randomised controlled trial of chronic intrathecal morphine administration supports effectiveness of this therapy for the management of chronic non-cancer pain.

Trial registration

International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

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INTRODUCTION

Opioid receptors were identified in the spinal cord in 1973.[1] Subsequent animal studies demonstrated that intrathecal opioids produce powerful and highly selective analgesia.[2] Intrathecal opioids exert their analgesic effect pre and post synaptically by reducing neurotransmitter release and by hyperpolarising the membranes of neurones in the dorsal horn, thus inhibiting pain transmission.[3]

The technique of intrathecal drug delivery is based on the principle that effective analgesia can be achieved by the action of some drugs at the dorsal horn and adequate concentrations cannot be achieved by systemic administration, or only by high systemic doses. Delivery of the drug by the intrathecal route is a means of achieving these enhanced therapeutic effects. The smaller doses needed for intrathecal administration also allow a reduction in side effects compared to systemic administration. Following the first clinical use of epidural [4] and intrathecal opioids,[5] Cousins used the expression 'selective spinal analgesia' to describe the phenomenon that spinally administered opioids could produce a specific analgesic effect with few motor, sensory or autonomic side effects.[6] It was subsequently demonstrated that the analgesic effect was, in the main, due to the uptake of the opioid directly into the spinal cord and cerebrospinal fluid.[3]

Key indications for intrathecal drug delivery systems are chronic pain unresponsive to curative medical or surgical measures and to more conservative palliative measures including systemic analgesics, physical therapies, psychological therapies, perineural injection procedures and nerve lesioning procedure. Pathologies for the pain are broad and only exclude psychogenic pains; they can be due to cancerous or non-malignant pathologies. Morphine is considered the 'gold standard' medication for intrathecal drug delivery systems because of its stability, receptor affinity and extensive experience of using the drug by this route.[7]

For chronic non-malignant pain it is strongly recommended that patients have a comprehensive psychological assessment [8] to: (i) assess possible concurrent psychopathology (e.g. severe affective disorder, body dysmorphia, procedural fears) that might impede successful implantation; and (ii) consider what additional individualised preparation might be advisable for the patient.[9] Cognitive behavioural therapy should not be excluded as a subsequent treatment option. It may ensure that the reduction in pain severity expected as a result of the ITDD system

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is capitalized upon by the development of reduced pain related behaviours and increased activity in a range of adaptive behaviours.

The first reservoir for intrathecal analgesic delivery was implanted in 1981,[10] and since then continuous intrathecal analgesia using opioids and other analgesics has become a recognized therapy for the management of severe and otherwise intractable chronic pain despite a lack of well-controlled studies. A three-year prospective study of intrathecal opioid treatment for chronic non-cancer pain showed that when patients with extremely severe pain problems are selected for intrathecal drug delivery, they are likely to improve with the therapy but their overall severity of pain and symptoms still remains high.[11] At least minimally clinical important changes in pain intensity were observed in 95% of participants in a recent study with a mean follow-up duration of 13 years.[12] Improvements were also observed in sensory and psychosocial outcomes.

Recent systematic reviews were unable to find randomised controlled trials (RCTs) evaluating the effectiveness of long-term intrathecal drug delivery systems (IDDS) for the management of chronic non-cancer pain.[13,14] Overall, the use of intrathecal opioid administration seems beneficial but the current available literature is too sparse to draw definite conclusions mainly due to the quality of the evidence. A systematic review of multiple well-designed RCTs is considered the highest level of evidence for the efficacy of a pain treatment, followed by a well-designed RCT of adequate size as the next best level of evidence.[15] To our knowledge there is only one such study of intrathecal opioids and that is confined to cancer pain.[16]

In the absence of strong supporting evidence for the use of intrathecal opioids for chronic non-cancer pain, the therapy must be balanced against its risks as catheter, procedure, device-related and illness-associated adverse incidents occurred at a rate of 0.45 events per patient year.[17] Furthermore, less common but serious events of permanent neurological injury can occur due to development of opioid associated granulomata. The incidence for this adverse event has been reported as 0.04% after one year, increasing to 1.15% after six years.[18]

We had previously undertaken a prospective controlled study, of single dose morphine compared with saline in patients with chronic non-malignant pain and demonstrated spinal morphine to be efficacious in the short term for patients who respond to systemic morphine but in whom side effects have become intolerable.[19] The current study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the

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intrathecal opioid dose following long-term administration would increase the level of pain intensity. Our primary outcome was visual analogue pain score change and withdrawal from study due to lack of efficacy.

METHODS

Study design and participants

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462). We conducted a single centre, double-blind, equal randomization [1:1], dose reduction, controlled, parallel group study. All subjects provided written informed consent. The original protocol anticipated using diamorphine, but between trial approval and trial commencement, practice changed to using morphine and the protocol was amended to reflect this.

At our centre patients are assessed by a multidisciplinary team including a clinical psychologist. Where there is discrepancy across the clinical team of physician, physiotherapist, psychologist and specialist nurse, a case conference is set up to include the family physician, and other psychologists, physiotherapists and physicians not directly involved in intrathecal therapy.

Following multidisciplinary assessment all patients have an inpatient trial of intrathecal therapy prior to implantation. This is conducted by repeated bolus of morphine and saline in a single blind fashion.[19] Patients reporting greater than 50% relief with morphine and less with saline are selected for IDDS. Chronic dosing is extrapolated and titrated at refills. A small increase in opioid dose may be necessary to maintain an adequate pain control. Recent observations indicate that significant differences cease following year 3 of therapy suggesting stability.[12] Adjuvant intrathecal medication such as bupivacaine may contribute to maintain low intrathecal morphine doses in cancer [20] and non-cancer patients.[21]

Eligible participants were adults aged 18 or over with implanted intrathecal reservoirs of programmable type (Synchromed, Medtronic Ltd) receiving intrathecal morphine for non-cancer pain and having had infusion for ≥ 12 months. Patients had reported a stable level of analgesia with the pump, based upon their attendance for pump refills at which dose did not change and they reported analgesia. In view of the need for weekly attendance during the study only those

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patients living within a short time journey from the hospital, with access to transport and limited co-morbidities were considered.

The pain nurse approached eligible patients for consent and patients were randomly assigned by computer generated randomization (PN) to one of two parallel groups in which one of the groups had no change in the morphine dose (control group) and the other group had a small reduction (20%) in dosage every week during participation in the study (intervention group). The allocation sequence was received in sequentially numbered, opaque and sealed envelopes to ensure that the sequence was concealed. Patients were unaware as to which group they were in, as the dose alteration or no change was conducted by telemetry with the screen not visible to the patient. The telemetry was conducted by a physician (JHR) who was the only investigator aware of the allocation. Pain scores and other outcome measures were collected by a researcher (RVD) blinded to the allocation of the patients.

Outcome measures

Primary outcome measures were visual analogue scale (VAS) [22] score for pain and withdrawal from study. Secondary outcome measures were functional and psychological measures based on Oswestry Disability Index (ODI),[23] Hospital Anxiety and Depression scale (HAD)[24] and Coping Strategies Questionnaire (CSQ).[25] Subjects were evaluated at baseline and each week during participation in the study. VAS and ODI were collected on a weekly basis. HAD and CSQ were collected fortnightly.

Patients were asked to rate their average pain intensity during the previous week using a VAS. The VAS consists of a 100 mm straight line with anchors at its ends labelled as no pain and worst pain imaginable. The VAS is a recognised method for the assessment in variation of pain intensity.[22,26] Clinically important changes were classified in accordance with a consensus statement that established a 10-20% decrease as minimally important, ≥ 30% as moderately important and ≥ 50% as a substantial change.[27]

The ODI is used to assess the level of pain interference with various activities of daily living. The ODI is a valid measure of condition-specific disability.[28] The ODI consists of 10 items/activities with 6 levels (range 0-5). Scoring of this questionnaire was calculated as recommended by Fairbank and Pynsent.[28]

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The HAD scale is a self-report rating scale of 14 items with 4 levels (range 0-3). This scale is used to screen for anxiety and depression (7 intermingled items for each subscale). The total score for each subscale is the sum of the respective seven items (ranging from 0–21). The HAD scale is considered a valid instrument for detecting states of anxiety and depression.[29]

The CSQ is a self-report instrument to assess active and passive coping skills of chronic pain patients.[30] The CSQ includes cognitive coping strategies (diverting attention, reinterpreting pain sensation, catastrophising, ignoring pain sensations, praying or hoping, coping self-statements), behavioural coping strategies (increasing activity level), and effectiveness ratings (control over pain, ability to decrease pain). Scores of these subscales result in 3 factors that account for 68% of the variance in questionnaire responses (cognitive coping and suppression, helplessness, diverting attention and praying). This questionnaire is a valid and reliable tool for chronic pain patient assessment.[25]

Data analysis

An *a priori* power analysis based on previous open study data of reduction in VAS for pain with intrathecal therapy computed a sample size of 24 (12 per group) would provide 80% power at the 5% significance level to detect a difference in the means of 1.2 standard deviations (unpaired t test) or a difference between the two proportions 20% and 80% (Fisher's Exact Test). Imputation methods were not used since the drop-out rate in the group randomised to have intrathecal dose reduction was 70%. This high drop-out percentage rate would bias the results regardless of the imputation technique employed. Therefore, all subjects were included in the analysis and this needed to be limited to between-group comparisons of baseline and final observation scores.

Kolmogorov-Smirnov test was performed to test normality of numerical data. The majority of the numerical data was not normally distributed and attempts to transform the data were unsuccessful. Therefore, differences between patient baseline characteristics were performed using the Mann-Whitney U test. Differences between baseline and last observation scores were evaluated using Wilcoxon Signed Ranks test. Categorical variables were investigated using Fisher's exact test. Data is reported as median (minimum-maximum). Statistical significance was judged at 5% level. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0, SPSS Inc., Chicago, IL, USA).

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RESULTS

Between 2006 and 2011, 24 patients were assessed for eligibility, nine declined to participate. Following inclusion in the study of 15 patients, it was observed that a high rate of patients withdrew from the research (Figure 1). Because of the large number of withdrawals, a first interim analysis was undertaken just beyond half way point which revealed that the withdrawals were all from the group randomised to have dose reduction. One subject left the study following week 1, three patients withdrew after week 2, two participants after week 5 and one patient after week 7. The intrathecal opioid dose in the patients that withdrew from the study was reduced from a median of 1.6 mg/day (0.625 – 5.5) to 1.15 mg/day (0.4 – 2.8) which corresponds to a decrease of 36% (20 - 79) in the intrathecal opioid dose. The reason for drop-out from the study was related with worsening of pain for all the participants. Calculation of drop-out rate between the groups indicated a significant statistical difference (p = 0.026). Recruitment ceased at that moment.

(Insert Figure 1/flow diagram here)

The patients recruited comprised 8 men (53.3%) and 7 women (46.7%) with a median age at the moment of enrolment in the study of 58 years (45-68). The median duration of IDDS therapy prior to participation in this study was 26 months (12-180). The pain syndrome was mechanical nociceptive caused by degenerative low back pain in 5 (33.3%) of the participants; visceral nociceptive due to post surgery abdominal pain in 1 (6.7%) patient and mixed nociceptive-neuropathic following failed back surgery syndrome in 9 (60%) subjects. The 5 patients in the control group comprised 2 with mechanical back pain and 3 with failed back surgery syndrome; the 10 in the intervention group comprised 3 with mechanical back pain, 6 with failed back surgery syndrome and 1 with post-surgery abdominal pain. All patients had been on systemic opioids prior to pump implantation and thereafter only took opioids intrathecally. The preparations differed and the equivalent oral morphine dose prior to implant ranged from 20 to 240mg morphine equivalent per day (Table 1 and 2).

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Table 1. Baseline characteristics of the patients according to randomization group

Characteristic	Control group (n = 5)	Intervention group (n = 10)	Test statistic	P
Age (years)	55 (45 - 59)	64 (52 - 68)	Z = -1.719	0.095
Gender (M/F)	4/1	4/6		0.282
Duration of therapy (months)	66 (22 - 88)	20.5 (12 - 180)	Z = -1.191	0.265
Pre-implant oral morphine dose mg/day	60 (20 - 120)	50 (40 - 240)	Z = -0.638	0.579
Morphine dose mg/day	4.625 (2.125 - 5.65)	1.612 (0.625 – 5.5)	Z = -2.205	0.028
Adjuvant intrathecal medication (Y/N)	4/1	5/5		0.580
Bupivacaine dose mg/day	3.190 (2.05 - 4.433)	2.050 (1.65 - 2.122)	Z = -1.715	0.111
Visual Analogue Scale	59 (0 - 69)	49.5 (10 - 64)	Z = -1.043	0.323
Oswestry Disability Questionnaire	54 (12 - 64)	55.85 (42 - 72)	Z = -0.677	0.529
Hospital Anxiety and Depression scale				
HAD anxiety	8 (2 - 16)	7.5 (1 - 12)	Z = -0.369	0.745
HAD depression	7 (2 - 11)	7.5 (2 - 15)	Z = -0.802	0.450
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	11.5 (0 - 31)	Z = -0.147	0.918
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.477	0.690
Catastrophising	7 (2 - 31)	22 (1 - 27)	Z = -0.147	0.911
Ignoring pain sensations	8 (3 - 21)	8 (0 - 28)	Z = -0.221	0.862
Praying or hoping	14 (2 - 26)	18.5 (0 - 30)	Z = -0.366	0.753
Coping self-statements	25 (15 - 30)	19 (2 - 32)	Z = -0.954	0.375
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.366	0.753
Control over pain	2 (1 - 5)	3 (1 - 4)	Z = -0.301	0.757
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -0.846	0.543
Cognitive coping and suppression	32 (18 - 70)	32.5 (6 - 83)	Z = -0.293	0.833
Helplessness	-7 (-14 - 10)	2 (-36 - 11)	Z = -0.806	0.458
Diverting attention and praying/hoping	26 (2 - 54)	31.5 (0 - 56)	Z = -0.440	0.698

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented *p* < 0.05

There were no statistically significant differences between the groups at baseline for age, gender, duration of therapy prior to study, adjuvant intrathecal medications, VAS, ODI, HAD scale and CSQ (Table 1). The intrathecal opioid dose administered at study entry was significantly higher in the control group (*Mdn* = 4.625) than in the intervention group (*Mdn* = 1.612), a chance finding, *U* = 7.00, *p* = 0.028, *r* = -0.57. A comparison of baseline scores between patients who completed the study and those that did not complete demonstrates non-

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significant differences for all the variables, including intrathecal dose administered at start of investigation (Table 2).

Table 2. Baseline characteristics of the patients according to completion of study

Characteristic	Complete (n = 8)	Incomplete (n = 7)	Test statistic	P
Age (years)	56.5 (45 - 68)	64 (53 - 66)	Z = -1.102	0.296
Gender (M/F)	6/2	2/5		0.132
Duration of therapy (months)	25 (15 - 88)	27 (12 - 180)	Z = -0.081	0.960
Pre-implant oral morphine dose mg/day	60 (20 - 120)	60 (40 - 240)	Z = -0.241	0.869
Morphine dose mg/day	3.065 (1.02 - 5.65)	1.6 (0.62 – 5.5)	Z = -1.273	0.232
Adjuvant intrathecal medication (Y/N)	5/3	4/3		1.000
Bupivacaine dose mg/day	2.5 (1.7 – 4.25)	2.085 (1.86-2.12)	Z = -0.735	0.556
Visual Analogue Scale	44.5 (0 - 69)	54 (23 - 64)	Z = -0.522	0.632
Oswestry Disability Index	53 (12 - 64)	57.7 (42 - 72)	Z = -1.222	0.244
Hospital Anxiety and Depression scale				
HAD anxiety	7 (2 - 16)	8 (1 - 12)	Z = -0.116	0.934
HAD depression	9 (2 - 15)	7 (2 - 12)	Z = -0.816	0.447
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	13 (0 - 31)	Z = -0.501	0.649
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.466	0.714
Catastrophising	22 (2 - 31)	15 (1 - 27)	Z = -0.575	0.608
Ignoring pain sensations	8 (0 - 21)	8 (0 - 28)	Z = -0.215	0.861
Praying or hoping	15 (2 - 30)	18.5 (0 - 25)	Z = -0.358	0.760
Coping self-statements	24 (13 - 30)	19 (2 - 32)	Z = -0.358	0.755
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.143	0.916
Control over pain	2 (1 - 5)	3.5 (2 - 4)	Z = -1.101	0.317
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -1.050	0.386
Cognitive coping and suppression	32 (12 - 70)	32.5 (6 - 83)	Z = -0.000	1.000
Helplessness	-5 (-14 - 11)	0 (-36 - 10)	Z = -0.215	0.868
Diverting attention and praying/hoping	27 (2 - 54)	31.5 (0 - 56)	Z = -0.287	0.809

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented $p < 0.05$

Statistically significant differences for VAS were observed between baseline and last observation in the group randomised to have dose reduction (intervention) but not in the control group (p = 0.188) (Table 3). The VAS was significantly lower at baseline (*Mdn* = 49.5) than at last observation (*Mdn* = 77.5) for the intervention group, Z = -2.805, p = 0.002, r = -0.627 (Figure 2).

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Table 3. Baseline and last observation scores for VAS and ODI

		VAS	ODI
Control group	Baseline	59 (0 - 69)	54 (12 - 64)
	Last observation	70 (40 - 83)	64 (30 - 74)
	Test statistic	$Z = -1.625$	$Z = -2.032$
	P	0.188	0.063
Intervention group	Baseline	49.5 (10 - 64)	55.85 (42 - 72)
	Last observation	77.5 (57 - 100)	68 (48 - 84)
	Test statistic	$Z = -2.805$	$Z = -2.201$
	P	0.002	0.027

(Insert Figure 2 here)

The ODI scores at baseline (*Mdn* = 55.85) were significantly lower than at last observation (*Mdn* = 68.40) for the group allocated to have dose reduction, $Z = -2.201$, $p = 0.027$, $r = 0.492$. No statistically significant differences were observed for the ODI in the control group ($p = 0.063$). There were no statistically significant changes detected for HAD scale anxiety and depression and all items of CSQ in either randomised group between baseline score and final observation. The VAS change between baseline and last observation was lower in the control group (Mdn = 11) than in the intervention group (Mdn = 30.5), although not statistically significant, $Z = -1.839$, $p = 0.070$, $r = -0.47$.

The calculation of clinical changes based on the VAS scores indicated non-significant clinical changes in 10% of the patients in the dose reduction group (intervention), minimally clinically important changes (≥10% and <30%) were observed in 20% of the participants randomised to this group, moderately important increase in pain (≥30% and <50%) in 40% of the subjects and substantially important increase in pain (≥50%) in 30% of the patients. For the group where the morphine dose remained the same (control), non-significant changes were observed in 40% of the sample, minimally clinically important changes (≥10% and <30%) in 40% of the participants and one patient (20%) had a clinically substantial increase in pain.

DISCUSSION

This randomised controlled trial of intrathecal opioid therapy in chronic non-malignant pain has demonstrated a significant difference in pain relief between dose reduction and dose maintenance. It lends support to the efficacy of this therapy, which until now has not been subject to controlled trials.

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A power analysis indicated that 24 patients would need to be included in the study to obtain a power of 0.8; however, due to high number of withdrawals, we undertook an interim analysis in which we found that the withdrawals were all in the dose reduction arm. Statistically significant differences between the arms were observed and the study was stopped. VAS and ODI differences were statistically significant between baseline and last observation for the treatment arms with statistically significant greater pain and worsened disability in the dose reduction arm. Clinically important changes indicating an increase in pain intensity were observed in 90% of the patients randomised to dose reduction (intervention). These changes were moderately important (≥30% and <50%) in 40% of the patients and substantially important (≥50%) in 30% of the participants.

Significant differences between groups at enrolment were observed for morphine dose. The dose maintenance group (control) were found to have a significantly higher starting opioid dose. This mirrored the statistically insignificant trend towards longer duration of intrathecal therapy. It is possible that this group had greater levels of pain than the intervention group for the same dose of opioid and/or that with longer duration of therapy, the dose had increased with time, as a small increase in opioid dose may be necessary to maintain an adequate pain control and recent observations from our unit indicate that significant differences cease following year 3 of therapy suggesting stability.[12] When dose escalation occurs, it is usually due to tolerance, progress of the disease [31] or opioid induced hyperalgesia.[32]

All subjects had stable levels of opioid delivery as evidenced by no change in delivered dose at recent refills before investigation and all reported analgesia with comparable pain scores (VAS). In using percentage dose reduction in this study, we anticipated overcoming a potential bias from this. Furthermore, no significant differences were observed at enrollment between those who completed the study and those who withdrew before completion, indicating that the initial opioid dose did not impact on drop-out rate. We had purposely chosen a small decrease of dose (20%) to avoid the patients suffering any withdrawal symptoms and none occurred. This parallels the experience of Rauck and colleagues in a study of opiate reduction within the context of investigating ziconotide.[33] In this study there was a 3 week weaning period prior to entering the trial and thus the weekly reduction in IT opioids would therefore be approximate to 30%. The weaning process was successful in 92.9% of the patients, only 14 dropped out due to inability to tolerate withdrawal, adverse events, noncompliance or patients request.

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This study has recognised weaknesses of small sample size and being conducted in a single centre. The sample size was inferior to the 24 patients indicated by the a priori power analysis as the study was stopped when an interim analysis was conducted due to large number of drop-outs and revealed significant differences for withdrawals between groups. This RCT was conducted in a single centre. Selection for therapy followed the national guidelines;[8] however, their interpretation may vary in clinical practice even within the same country in the psychosocial domains of pain. Dose titration strategies may differ across treatment centres. Different centres have reported average doses of 4.7 mg/day at an average of 3.4 years,[34] 7.42 mg/day at 29.14 months,[35] 9.6 mg/day at year 1 [36] and 12.2 mg/day at year 3.[37] This may lead to different levels of opioid delivery for which the sensitivity to dose reduction may differ.

The strengths of this study were not looking in the period following intrathecal drug delivery implantation because we considered that this period is confounded by need for dose titration and the non-specific psychological effects of a major intervention. In investigating patients with intrathecal delivery for a minimum of 12 months, we have been able to focus on evaluation of long term efficacy of intrathecal opioid therapy. To our knowledge this is the first randomised double-blind controlled study of this therapy in non-cancer pain. The findings of our randomised controlled trial support the efficacy of intrathecal morphine for the management of chronic non-cancer pain. Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction. In the light of these results, investigation of different populations and larger cohorts are recommended.

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Figure legends

Figure 1. Flow chart of patient participation

Figure 2. Individual visual analogue scale scores at baseline and final observation for control

group (n=5) and reduction group (n=10).

Acknowledgments

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Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

JHR designed and was responsible for the conception of the trial. JHR, RVD, JLS, PN, GDK have made substantial contributions to (1) the acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

Data sharing

No additional data is available.

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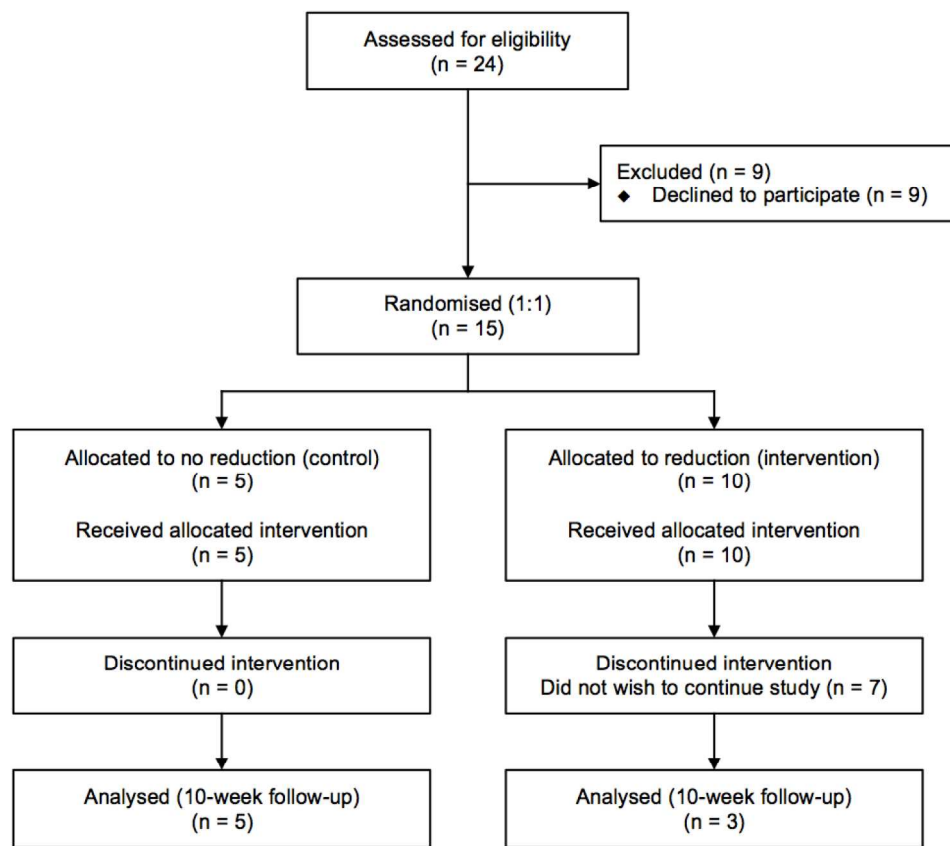48
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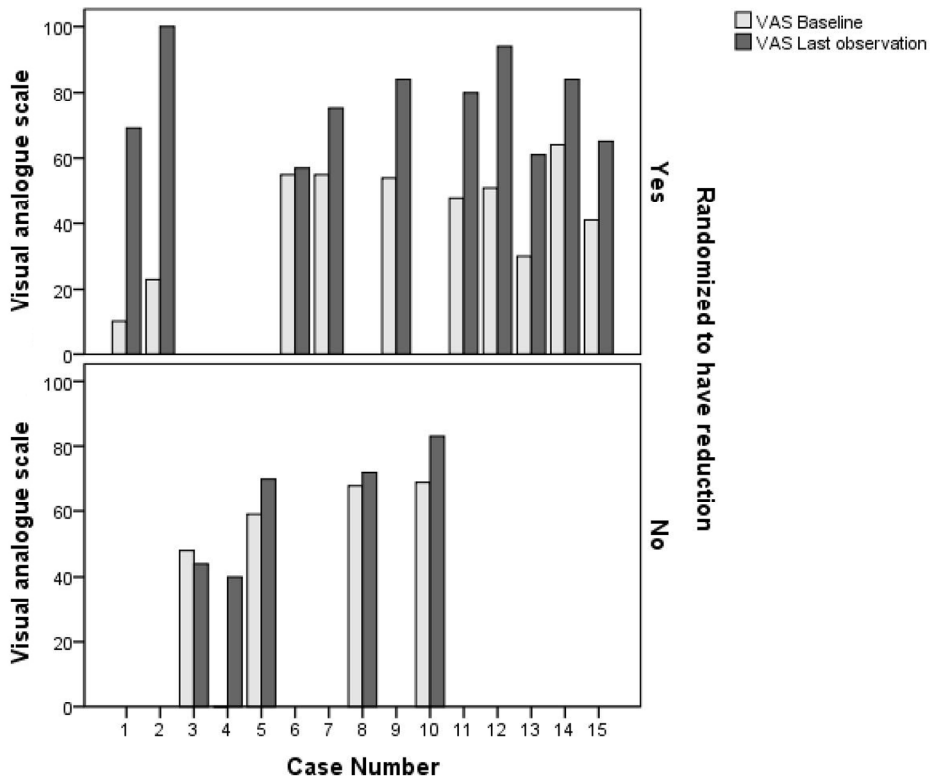Figure 1. Flow chart of patient participation
360x310mm (300 x 300 DPI)

Figure 2. Individual visual analogue scale scores at baseline and final observation for control group (n=5) and reduction group (n=10)
441x353mm (300 x 300 DPI)

Birmingham and The Black Country **NHS**
Health Authority

Dudley Local Research Ethics Committee
Chair: Chris Spencer-Jones
E-mail: chris.spencer-jones@dudley.nhs.uk
Administrator: Tracey Hartle
Direct Dial: 01384 366033
E-mail: tracey.hartle@dudley.nhs.uk

12 Bull Street
Dudley
West Midlands
DY1 2DD

Tel: 01384 239376
Fax: 01384 455068

REC/38/02/JUN   **Please quote this number on all correspondence**

23 July 2002

Dr J Raphael
Consultant in Pain Management
Russells Hall Hospital
DUDLEY
West Midlands
DY1 2HQ

Dear Dr Raphael

Research Protocol: REC/38/02/JUN; Randomised controlled trial of intrathecal diamorphine in the treatment of chronic non-malignant pain

The Dudley REC reviewed your application on Friday 21 June 2002. The documents reviewed were as follows:

- **Application Form (No Version Dated: 04/04/02)**
- **Patient information sheet and consent form (No Version No Date)**
- **Questionnaire (No Version No Date)**

The members of the Committee present agreed there is no objection on ethical grounds to the proposed study. I am, therefore, happy to give you the favourable opinion of the committee on the understanding that you will follow the conditions set out below:

Conditions

- You do not recruit any research subjects within a research site unless favourable opinion has been obtained from the relevant REC.

- You do not undertake this research in an NHS organisation until the relevant NHS management approval has been gained as set out in the Framework for Research Governance in Health and Social Care.

Minicom: (Text Phone Users) 01384 243187
DX: 709411 Dudley 5

2
REC/35/02/JUN

- You do not deviate from, or make changes to, the protocol without prior written approval of the REC, except where this is necessary to eliminate immediate hazards to research participants or when the change involves only logistical or administrative aspects of the research. In such cases the REC should be informed within seven days of the implementation of the change.

- You complete and return the standard progress report form to the REC one-year from the date on this letter and thereafter on an annual basis. This form should also be used to notify the REC when your research is completed and in this case should be sent to this REC within three months of completion.

- If you decided to terminate this research prematurely you send a report to this REC within 15 days, indicating the reason for the early termination.

- You advise the REC of any unusual or unexpected results that raise questions about the safety of the research.

- Note that the LREC approval is necessary but not sufficient for you to undertake this research project within your local NHS organisation and you will require separate approval from your organisation's Research and Development Directorate/ management in accordance with the research governance framework. Care should also be taken to ensure with the NHS organisation that local indemnity arrangements are adequate.

Any comments the REC wished to make are contained in the attached REC Response Form. The project must be started within three years of the date on this letter.

Yours sincerely

Dr Chris Spencer-Jones
CHAIR

cc   Mrs M Marriott, R & D Department

RESEARCH ETHICS COMMITTEE
RESPONSE FORM

DETAILS OF APPLICANT:

1.   **Name and address of Principal Researcher:** Dr Jon Raphael, Consultant in
       Pain Management, Russells Hall Hospital, Dudley, West Midlands

2.   **Title of project:** Randomised controlled trial of intrathecal diamorphine in the
       treatment of chronic non-malignant pain

3.   **Name and address of Sponsor:**

DETAILS OF REC:

4.   **Name and address of REC:** Dudley REC, 12 Bull St, DUDLEY, West Midlands

5.   **REC Reference Number:** REC/38/02/JUN

**Listed below is a complete record of the review undertaken by REC with the decisions
made, dates of decisions and the requirements at each stage of the review:**

21/06/02

- *It was agreed that the design of this research application was sound and should
  provide useful information. There was a question of the practicalities of using
  diamorphine which is unstable and can be made up locally vs morphine that is
  stable and can be prepared in sterile conditions. The committee asked Dr Raphael
  to look into past infection rates using pumps and if there is a case for using sterile
  preparations. Any risk should be discussed with the Trust's Clinical Governance
  Department. Should there be a case for using morphine Dr Raphael should liaise
  with Ron Pate*

THE FINAL DOCUMENTS AND ARRANGEMENTS APPROVED BY THE REC

The following items have been approved by the Dudley REC:

Protocol [No Version Dated: 04/04/02]
Subject information sheet [No Version No Date]
Subject consent form [No Version No Date]
Subject questionnaire [No Version No Date]

Date of approval: **June 21 2002**

Signature of Chair/Administrator: Date:

Name *(please print)*:   DR CHRIS SPENCER JONES

DUDLEY PAIN MANAGEMENT SERVICE

Jon Raphael MD MSc (Pain)
Consultant in Pain Medicine

Secretary: Miss Julie Hackett
Tel No: 01384 244809
Fax No: 01384 244808
Helpline: 01384 244735
Email: Julie.hackett@dgoh.nhs.uk

JR/JH

27 January 2005

Dr J Neilson
Chairman
Research Ethics Committee
Haematology Department
Russells Hall Hospital

Dear Jeff

**REC/38/02/JUN. RANDOMISED CONTROLLED TRIAL OF
INTRATHECAL DIAMORPHINE IN THE TREATMENT OF CHRONIC
NON MALIGNANT PAIN**

In the middle of 2004 there was a directive from the Medical Devices Agency that
recommended Diamorphine no longer be used in intrathecal programmable pumps
because of a few reports of mechanical pump failure. It was thought that this was
related to the mono acetate metabolite of Diamorphine. Accordingly we are following
the recommendations of the Pain Society and all new implanted pumps are now filled
with Morphine and we are in the process of converting the existing pumps from
Diamorphine to Morphine. As you will appreciate since April 2004 we have not
recruited anybody to this study. We would, however, like to continue with this
research in respect of intrathecal Morphine as opposed to Diamorphine. Since
Diamorphine very rapidly breaks down to Morphine and when administered
intrathecally they are equivalent in dose (as shown in publication with Mourad Labib) we
would like to continue with the same protocol except but substituting the word
Diamorphine for Morphine throughout. The design of the study is a percentage dose
reduction protocol, the reported efficacy and side effects of intrathecal Morphine are
same as Diamorphine and therefore, we do not require to change the protocol in other
respect. I look forward to hearing from you.

With kind regards,
Yours sincerely

dictated but not signed

Jon Raphael MD MSc (Pain)
Consultant in Pain Medicine

**DESCRIPTION OF RESEARCH PROJECT FOR SUBMISSION TO THE DUDLEY LOCAL
RESEARCH ETHICS COMMITTEE**

NOTE: ALL QUESTIONS MUST BE ANSWERED BY THE PERSON ACTUALLY UNDERTAKING
THE RESEARCH.
ANSWERS MUST BE TYPEWRITTEN. ANY FORMS NOT COMPLETED IN TYPE
WILL BE RETURNED

1   Name(s) of Responsible Investigator(s):-

Jointly_
Jon Raphael, Consultant in Pain Management, Dudley GOH
David Booth, Professor of Psychology, Univ of Birmingham
George Kitas, Consultant Rheumatologist, Dudley GOH

2   Please advise the number of other trials/studies in which the local investigator
a) is currently involved?
5

b) has been involved in the last six months?
as above

2a   Title of Project:-

Randomised controlled trial of intrathecal diamorphine in the treatment of chronic non-malignant pain

2b   Clinical Trial Certificate Reference or Exemption Certificate Reference:-

N/A

3a   Objective (i.e. hypothesis which it is intended to test):-

1. Intrathecal opioids are useful in the treatment of severe chronic non-
malignant pain

2. Therapeutic efficacy is dose-dependent

3. Gradual reduction of intrathecal opioid dose is safe

-1 -

3b   What practical benefit do you envisage from a successful completion of this project?

Production of evidence of good scientific quality that this therapeutic approach is useful (or not) in severe chronic non-malignant pain

Identification of the most appropriate diamorphine dose that should be used for treatment, with the minimum potential for side effects

4   Design of the Study (describe briefly):-

Patients will be recruited from those already with an implanted intrathecal drug delivery system providing diamorphine for chronic non-malignant pain.

All patients meeting above criteria will be approached for recruitment and those who consent to enter this study will be randomised by random numbers generator into one of two groups:

Group 1 will have the dose of diamorphine reduced every week by 20% of the preceeding weeks dose for 10 weeks.

week	dose (as percentage of starting dose)
0	100%
1	80
2	64
3	51
4	41
5	33
6	25.5
7	20.5
8	16.5
9	13
10	10

Group 2 has no change in dose at these weekly visits.
The above changes are made by computer telemetry to which patient is blinded.

Measurements will be made at these weekly visits as follows:
1. Pain will be measured using Visual Analogue Scale (VAS)
2. Function will be measured by the Ostwestry Disability Score (ODS)
3. Psychological parameters will be measured by the Hospital Anxiety Depression Score (HAD) and the Pain Coping Strategies Questionnaire (PCSQ)
4. Sociological parameters will be measured by the Short Form-36 Questionnaire (SF-36)
5. An overall assessment of change will be measured by the Global Impression of Change (GIC).

Endpoint will be withdrawal due to inefficacy or withdrawal due to side effects

-2 -

5a   Scientific background: give a brief account:-

Chronic non-malignant pain has enormous social and economic consequences (CSAG, 1994). A wide variety of treatments are used including drugs, physical therapies, operations and psychological treatments. Although they appear to help some patients and many have been subjected to studies that support their benefit, there remain a number of patients who continue despite this to have severe chronic and disabling pain.

The discovery of opioid receptors in the spinal cord led to the rationale use of intrathecal opioids for pain relief (Wang, 1979). This was initially used in those patients with cancer. With the development of implantable, programmable, continuous drug delivery systems in the 1980s, the use of intraspinal opioids was extended to non-cancer pain.

Published data on the outcome of this therapy is limited to retrospective studies from the USA (Paice, 1996), Europe (Winkelmuller, 1996) and the UK (Raphael, 2000). Nevertheless , these studies consistently support its benefits in alleviating pain and improving quality of life as reported by the National Institute of Clinical Excellence (NICE) (Williams, 2001). It also appears to be cost effective since less drugs and other treatments are needed after spinal pump implantation (Mueller-Schwefe, 1999).

The NICE document expressed the need for comparator studies to provide more robust data and I am in the process of designing a multi-centre prospective randomised placebo controlled trial to address this in new patients in liason with the Birmingham Clinical Trials Unit. However, a lot can be learnt from patients already receiving this therapy. These cannot be randomised in a placebo controlled trial because opioid withdrawal would lead to unacceptable side effects. They can be randomised to a dose-ranging trial as described above which will produce information about the efficacy (or not) of this therapy and the optimum dose.

5b   Has the investigation been done previously with human subject?

No

5c   If so, why repeat it?

6a   Subjects:How many are needed?

Power calculations have been based on previous open study with pain as primary outcome. 24 patients are required in total (12 per group) to provide 80% power at the 5% significance level

                and how selected?

-3 -

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5   Patients receiving intrathecal diamorphine for chronic non-malignant pain by implanted
6   computerised drug delivery system. As the regional centre for this therapy we have sufficient patients attending for
7   follow up to acheive the required sample size.
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12   **6b**   Are the patients included in this study involved in any other research investigation at the   present time?
13
14   No
15
16   **6c**   Controls: how many are needed?
17
18   12 (described above)
19
20
21   **6d**   What is the primary end point?
22   Pain relief by VAS
23   Withdrawal from protocol due to inefficacy
24
25
26
27   **7a**   Have you taken any statistical advice on the numbers required for your study to give   scientific
28   validity
29   YES
30
31
32   **7b**   If YES from whom was the advice obtained?
33
34   D. Booth, Professor of Health Psychology, Univ of Birmingham
35
36
37
38
39   **7c**   If NO why not?
40
41
42   N/A
43
44   **8a**   Substances to be given to the subjects (special diets, drugs, isotope tracers etc):-
45
46   **STATE ROUTE OF ADMINISTRATION, AMOUNT & EFFECTS ANTICIPATED:**
47
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50   N/A
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53   **8b**   Who will cover the costs of these substances?
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8c   How will they be stored and issued?

9a   Samples to be taken from the subjects (venepuncture, arterial, urine, biopsy etc):

STATE TYPE OF SAMPLE, FREQUENCY & AMOUNT: -

N/A

9b   Would the sample be taken especially for this investigation rather than as part of normal   patient care?

9c   If taken especially for this investigation who will cover the costs of these tests?

10   Other tests to be administered:-
Questionnaires as described earlier

11a   Will any additional staff or facilities be required?

No
11b   If so, who will meet the cost of these requirements?

N/A

12   Procedures: describe the exact procedure which will be applied to each patient:-

All patients with implanted intrathecal drug administration systems and diagnosis of severe chronic non-malignant pain will be approached for recruitment consecutively. The study will be explained to them by Dr Raphael (Pain Consultant) and Ms Southall(Pain Nurse Practitioner) verbally and they will also be given written information. They will be given opportunity to think about it, discuss it and ask any questions. Those who give consent to enter the study will be randomised by random number into one of the two groups described earlier. They will be required to attend the pain unit weekly for 10 weeks for approximately half an hour to undergo computerised telemetric reprogramming of the pump and complete questionnaires.

At the end of the 10 week period, patients can opt to remain on their current dose or return to a previous dose. This choice will form part of data collection.

As described in the protocol , patients can withdraw from the study at any stage without prejuding their treatment.

13   Discomfort: what discomfort or interference with their activities may be suffered by all   or   any of the patients?

-5 -

Patients required to attend the clinic weekly for the 10 week study period (compared to routine of attendance every 6-12 weeks) for pump dose change and completion of questionnaires. Estimated total time each at visit is 30 minutes

14a   Hazards: are there any physical or mental hazards associated with these investigations?

Potentially less pain relief

14b   If so, what are these?

As above

14c   How do you assess the chances of such hazards occurring:-

                                    Possible

15   In precisely what terms is it proposed to explain the project to potential subjects?

Patient information sheet(enclosed)

16a   Are any payments to be made for entering patients in this study? No
          If yes, how much?

16b   If so, to whom and how will the money be used. Please indicate as clearly as possible how the money generated from undertaking this trial will be utilised.

16c   It should be noted that any monies received by NHS clinicians for research carried out on patients in NHS facilities should be placed into accounts or Trust Funds which are available for financial audit.

Will the monies you receive be placed into an account available for audit?

                                    Yes
                                    No

If no what will happen to the monies received?

Your attention is drawn to paragraph 120 of the GMC guidelines, Professional Conduct and Discipline: Fitness to Practise -

-6 -

"It may be improper for a doctor to accept per capita or other payments from a pharmaceutical firm in relation to a research project such as the clinical trial of a new drug, unless the payments have been specified in a protocol for the project which has been approved by the relevant national or local ethical committee. It may be improper for doctors to accept per capita or other payments under arrangements for recording clinical assessments of a licensed medicinal product, whereby they are asked to report reactions which they have observed in patients for whom they have prescribed the drug, unless the payments have been specified in a protocol for the project which has been approved by the relevant national or local ethical committee. It is improper for doctors to accept payment in money or kind which could influence their professional assessment of the therapeutic value of a new drug."

17   Have you enclosed a specimen of written consent form?

        Yes

18   Is it your intention to inform the patient's G.P of his/her inclusion in the study?

        Yes

19a   Will patient medical records be examined by research member(s) outside the   employment   of   the
NHS?

        Yes. Psychologist

19b   If yes above what steps will be taken to safeguard confidence?

        Clinician investigator will obtain honorary contract for patient contact.

The information supplied above is to the best of my knowledge and belief accurate. I understand my obligations and the rights of the patient, particularly the need to obtain freely given written informed consent.

Date of Submission: Signature of Investigator:

   4/4/c2

....

To be completed by the Consultant in Charge or Head of Department

I have read through the study protocol and this form.
I hereby endorse this application with my approval:-

Signature: ....

-7-

CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	4.5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6,7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	8
	13b	For each group, losses and exclusions after randomization, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9.10
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

[a] We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

(Reprinted) JAMA, July 7, 2010—Vol 304, No. 1 **E1**

BMJ open

Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain

SCHOLARONE™
Manuscripts

Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain

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[4] Department of Rheumatology, Russells Hall Hospital, Dudley, UK

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Word count: 3,357

ABSTRACT

Objective

This study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity.

Design

Randomised, double blind, controlled, parallel group trial.

Setting

Department of Pain Management, Russells Hall Hospital, Dudley, United Kingdom.

Participants

Twenty-four non-cancer pain patients implanted with morphine reservoirs were assessed for eligibility.

Interventions

Participants were randomly allocated to one of two parallel groups in which one of the groups had no change in morphine dose and the other group had a small reduction (20%) in dosage every week during a 10-week follow-up.

Outcome

Primary outcomes were visual analogue scale (VAS) pain score change and withdrawal from study due to lack of efficacy.

Results

Nine of the patients assessed for eligibility declined to participate in the study. Fifteen patients were randomised to control (n=5) or intervention (n=10) and included in an intention-to-treat analysis. Due to worsening of pain, seven patients withdrew from the study prematurely. None knew prior to withdrawal which arm of the study they were in, but all turned out to be in the dose reduction arm. Calculation of drop-out rate between groups indicated a significant statistical difference (p=0.026) and recruitment was ceased. VAS change between baseline and last observation was smaller in the control group (Mdn=11) than in the intervention group (Mdn=30.5), although not statistically significant, Z=-1.839, p=0.070, r=-0.47. Within groups, VAS was significantly lower at baseline (Mdn=49.5) than at last observation (Mdn=77.5) for the reduction group, Z=-2.805, p=0.002, r=-0.627 but not for the control group (p=0.188).

Conclusion

This double blind RCT of chronic intrathecal morphine administration suggests effectiveness of this therapy for the management of chronic non-cancer pain. However, due to small number of patients completing the study (n=8) further studies are warranted.

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Trial registration

International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

INTRODUCTION

Opioid receptors were identified in the spinal cord in 1973.[1] Subsequent animal studies demonstrated that intrathecal opioids produce powerful and highly selective analgesia.[2] Intrathecal opioids exert their analgesic effect pre and post synaptically by reducing neurotransmitter release and by hyperpolarising the membranes of neurones in the dorsal horn, thus inhibiting pain transmission.[3]

The technique of intrathecal drug delivery is based on the principle that effective analgesia can be achieved by the action of some drugs at the dorsal horn and adequate concentrations cannot be achieved by systemic administration, or only by high systemic doses. Delivery of the drug by the intrathecal route is a means of achieving these enhanced therapeutic effects. The smaller doses needed for intrathecal administration also allow a reduction in side effects compared to systemic administration. Following the first clinical use of epidural [4] and intrathecal opioids,[5] Cousins used the expression 'selective spinal analgesia' to describe the phenomenon that spinally administered opioids could produce a specific analgesic effect with few motor, sensory or autonomic side effects.[6] It was subsequently demonstrated that the analgesic effect was, in the main, due to the uptake of the opioid directly into the spinal cord and cerebrospinal fluid.[3]

Key indications for intrathecal drug delivery systems are chronic pain unresponsive to curative medical or surgical measures and to more conservative palliative measures including systemic analgesics, physical therapies, psychological therapies, perineural injection procedures and nerve lesioning procedure. Pathologies for the pain are broad and only exclude psychogenic pains; they can be due to cancerous or non-malignant pathologies. Morphine is considered the 'gold standard' medication for intrathecal drug delivery systems because of its stability, receptor affinity and extensive experience of using the drug by this route.[7]

For chronic non-malignant pain it is strongly recommended that patients have a comprehensive psychological assessment [8] to: (i) assess possible concurrent psychopathology (e.g. severe affective disorder, body dysmorphia, procedural fears) that might impede successful implantation; and (ii) consider what additional individualised preparation might be advisable for the patient.[9] Cognitive behavioural therapy should not be excluded as a subsequent treatment

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option. It may ensure that the reduction in pain severity expected as a result of the ITDD system is capitalized upon by the development of reduced pain related behaviours and increased activity in a range of adaptive behaviours.

The first reservoir for intrathecal analgesic delivery was implanted in 1981,[10] and since then continuous intrathecal analgesia using opioids and other analgesics has become a recognized therapy for the management of severe and otherwise intractable chronic pain despite a lack of well-controlled studies. A three-year prospective study of intrathecal opioid treatment for chronic non-cancer pain showed that when patients with extremely severe pain problems are selected for intrathecal drug delivery, they are likely to improve with the therapy but their overall severity of pain and symptoms still remains high.[11] At least minimally clinical important changes in pain intensity were observed in 95% of participants in a recent study with a mean follow-up duration of 13 years.[12] Improvements were also observed in sensory and psychosocial outcomes.

Recent systematic reviews were unable to find randomised controlled trials (RCTs) evaluating the effectiveness of long-term intrathecal drug delivery systems (IDDS) for the management of chronic non-cancer pain.[13,14] Overall, the use of intrathecal opioid administration seems beneficial but the current available literature is too sparse to draw definite conclusions mainly due to the quality of the evidence. A systematic review of multiple well-designed RCTs is considered the highest level of evidence for the efficacy of a pain treatment, followed by a well-designed RCT of adequate size as the next best level of evidence.[15] To our knowledge there is only one such study of intrathecal opioids and that is confined to cancer pain.[16]

In the absence of strong supporting evidence for the use of intrathecal opioids for chronic non-cancer pain, the therapy must be balanced against its risks as procedure related complications have been reported to occur at a rate of 0.29 events per patient year and catheter related complications at a rate of 0.05 events per patient year.[17] Possible infections include meningitis, epidural abscess, pump pocket infection or pump reservoir infection. The rate of meningitis reported by studies ranged from 2.3% to 15.4% and for wound infections from 4.2% to 8.8%.[18] When considering only non-cancer pain studies, the percentage of patients with meningitis ranged from 0% to 4% and for wound infections, from 0% to 22%.[19] Furthermore, less common but serious events of permanent neurological injury can occur due to development of opioid associated granulomata. The incidence for this adverse event has been reported as 0.04% after one year, increasing to 1.15% after six years.[20] The management of the different

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adverse events is varied as some acute side-effects may resolve with time (e.g. nausea, vomiting, dizziness, or itching). Recommendations for aftercare, on-going care, prevention and management of potential complications and side-effects has been described.[8,18]

We had previously undertaken a prospective controlled study, of single dose morphine compared with saline in patients with chronic non-malignant pain and demonstrated spinal morphine to be efficacious in the short term for patients who respond to systemic morphine but in whom side effects have become intolerable.[21] The current study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity. Our primary outcome was visual analogue pain score change and withdrawal from study due to lack of efficacy.

METHODS

Study design and participants

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462). We conducted a single centre, double-blind, equal randomization [1:1], dose reduction, controlled, parallel group study. All subjects provided written informed consent. The original protocol anticipated using diamorphine, but between trial approval and trial commencement, practice changed to using morphine and the protocol was amended to reflect this.

Treatment strategies for the management of chronic pain start with the lowest risk and least invasive intervention and progress if a treatment is not effective. IDDS is a last-resort treatment to treat severe chronic pain because of their invasive nature, concerns about long-term opioid use, and the possible complications related to the procedure. IDDS is considered for use in patients with chronic non-cancer pain after more conventional treatments have failed (e.g. pharmacotherapy, transcutaneous electrical stimulation or in some cases spinal cord stimulation) and in those who respond to systemic opioids but the side effects have become intolerable. Patient suitability is also determined by a multidisciplinary team assessment that includes a clinical psychologist. A biopsychosocial history is performed, in which factors such as organic cause of pain, topography, duration of pain, pain intensity, coping strategies, social support, medico legal matters, history of anxiety and/or depression, previous treatments, and

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drug and/or alcohol abuse is taken into consideration. Where there is discrepancy across the clinical team of physician, physiotherapist, psychologist and specialist nurse, a case conference is set up to include the family physician, and other psychologists, physiotherapists and physicians not directly involved in intrathecal therapy.

Following multidisciplinary assessment all patients have an inpatient trial of intrathecal therapy prior to implantation. This is conducted by repeated bolus of morphine and saline in a single blind fashion.[21] Patients reporting greater than 50% relief with morphine and less with saline are selected for IDDS. Chronic dosing is extrapolated and titrated at refills (approximately two per month initially). A small increase in opioid dose may be necessary to maintain an adequate pain control. Recent observations indicate that significant differences cease following year 3 of therapy suggesting stability.[12] Additional intrathecal drugs were added if level of analgesia is inadequate as per polyanalgesic consensus conference algorithm.[22] Adjuvant intrathecal medication such as bupivacaine may contribute to achieve better pain control and to maintain low intrathecal morphine doses in cancer [23] and non-cancer patients.[24]

Eligible participants were adults aged 18 or over with implanted intrathecal reservoirs of programmable type (Synchromed, Medtronic Ltd) receiving intrathecal morphine for non-cancer pain and having had infusion for ≥ 12 months. Patients had reported a stable level of analgesia with the pump, based upon their attendance for pump refills at which dose did not change and they reported analgesia. In view of the need for weekly attendance during the study only those patients living within a short time journey from the hospital, with access to transport and limited co-morbidities were considered.

The pain nurse approached eligible patients for consent and patients were randomly assigned by computer generated randomization (PN) to one of two parallel groups in which one of the groups had no change in the morphine dose (control group) and the other group had a small reduction (20%) in the preceding week dose every week during participation in the study (intervention group). The allocation sequence was received in sequentially numbered, opaque and sealed envelopes to ensure that the sequence was concealed. Patients were unaware as to which group they were in, as the dose alteration or no change was conducted by telemetry with the screen not visible to the patient. The telemetry was conducted by a physician (JHR) who was the only investigator aware of the allocation. Pain scores and other outcome measures were collected by a researcher (RVD) blinded to the allocation of the patients.

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Outcome measures

Primary outcome measures were visual analogue scale (VAS) [25] score for pain and withdrawal from study. Secondary outcome measures were functional and psychological measures based on Oswestry Disability Index (ODI),[26] Hospital Anxiety and Depression scale (HAD)[27] and Coping Strategies Questionnaire (CSQ).[28] Subjects were evaluated at baseline and each week during participation in the study. VAS and ODI were collected on a weekly basis. HAD and CSQ were collected fortnightly.

Patients were asked to rate their average pain intensity during the previous week using a VAS. The VAS consists of a 100 mm straight line with anchors at its ends labelled as no pain and worst pain imaginable. The VAS is a recognised method for the assessment in variation of pain intensity.[25,29] Clinically important changes were classified in accordance with a consensus statement that established a 10-20% decrease as minimally important, ≥ 30% as moderately important and ≥ 50% as a substantial change.[30]

The ODI is used to assess the level of pain interference with various activities of daily living. The ODI is a valid measure of condition-specific disability.[31] The ODI consists of 10 items/activities with 6 levels (range 0-5). Scoring of this questionnaire was calculated as recommended by Fairbank and Pynsent.[31]

The HAD scale is a self-report rating scale of 14 items with 4 levels (range 0-3). This scale is used to screen for anxiety and depression (7 intermingled items for each subscale). The total score for each subscale is the sum of the respective seven items (ranging from 0–21). The HAD scale is considered a valid instrument for detecting states of anxiety and depression.[32]

The CSQ is a self-report instrument to assess active and passive coping skills of chronic pain patients.[33] The CSQ includes cognitive coping strategies (diverting attention, reinterpreting pain sensation, catastrophising, ignoring pain sensations, praying or hoping, coping self-statements), behavioural coping strategies (increasing activity level), and effectiveness ratings (control over pain, ability to decrease pain). Scores of these subscales result in 3 factors that account for 68% of the variance in questionnaire responses (cognitive coping and suppression, helplessness, diverting attention and praying). This questionnaire is a valid and reliable tool for chronic pain patient assessment.[28]

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Data analysis

An *a priori* power analysis based on previous open study data of reduction in VAS for pain with intrathecal therapy [21] computed a sample size of 24 (12 per group) would provide 80% power at the 5% significance level to detect a difference in the means of 1.2 standard deviations (unpaired t test) or a difference between the two proportions 20% and 80% (Fisher's Exact Test). The power analysis was based on a study which compared one group receiving morphine with one group receiving placebo (saline). The difference in means in the pilot study (5.1-0.91 = 4.19) was not used as the basis for the power calculation as the difference in the pilot study was likely to be larger than the difference observed in the current study where both groups received morphine. A difference in the means of 1.2 standard deviations was considered as a realistic estimate since we allowed for the effect to be much smaller than that observed in the pilot study (2.6 standard deviations if the standard deviations of 1.3 and 1.9 are pooled). Imputation methods were not used since the drop-out rate in the group randomised to have intrathecal dose reduction was 70%. This high drop-out percentage rate would bias the results regardless of the imputation technique employed. Therefore, we followed an intention-to-treat protocol; all subjects were included in the analysis and this was limited to within and between-group comparisons of baseline and final observation scores.

Kolmogorov-Smirnov test was performed to test normality of numerical data. The majority of the numerical data was not normally distributed and attempts to transform the data were unsuccessful. Therefore, differences between patient baseline characteristics were performed using the Mann-Whitney U test. Differences between baseline and last observation scores were evaluated using Wilcoxon Signed Ranks test. Categorical variables were investigated using Fisher's exact test. Data is reported as median (minimum-maximum). Statistical significance was judged at 5% level. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0, SPSS Inc., Chicago, IL, USA).

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RESULTS

Between 2006 and 2011, 24 patients were assessed for eligibility, nine declined to participate. Following inclusion in the study of 15 patients, it was observed that a high rate of patients withdrew from the research (Figure 1). Because of the large number of withdrawals, a first interim analysis was undertaken just beyond half way point which revealed that the withdrawals were all from the group randomised to have dose reduction. One subject left the study following week 1, three patients withdrew after week 2, two participants after week 5 and one patient after week 7. The intrathecal opioid dose in the patients that withdrew from the study was reduced from a median of 1.6 mg/day (0.625 – 5.5) to 1.15 mg/day (0.4 – 2.8) which corresponds to a decrease of 36% (20 - 79) in the intrathecal opioid dose. The reason for drop-out from the study was related with worsening of pain for all the participants. Calculation of drop-out rate between the groups indicated a significant statistical difference (p = 0.026). Recruitment ceased at that moment.

(Insert Figure 1/flow diagram here)

The patients recruited comprised 8 men (53.3%) and 7 women (46.7%) with a median age at the moment of enrolment in the study of 58 years (45-68). The median duration of IDDS therapy prior to participation in this study was 26 months (12-180). The pain syndrome was mechanical nociceptive caused by degenerative low back pain in 5 (33.3%) of the participants; visceral nociceptive due to post surgery abdominal pain in 1 (6.7%) patient and mixed nociceptive-neuropathic following failed back surgery syndrome in 9 (60%) subjects. The 5 patients in the control group comprised 2 with mechanical back pain and 3 with failed back surgery syndrome; the 10 in the intervention group comprised 3 with mechanical back pain, 6 with failed back surgery syndrome and 1 with post-surgery abdominal pain. All patients had been on systemic opioids prior to pump implantation and thereafter only took opioids intrathecally. The preparations differed and the equivalent oral morphine dose prior to implant ranged from 20 to 240mg morphine equivalent per day (Table 1 and 2).

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Table 1. Baseline characteristics of the patients according to randomization group

Characteristic	Control group (n = 5)	Intervention group (n = 10)	Test statistic	P
Age (years)	55 (45 - 59)	64 (52 - 68)	Z = -1.719	0.095
Gender (M/F)	4/1	4/6		0.282
Duration of therapy (months)	66 (22 - 88)	20.5 (12 - 180)	Z = -1.191	0.265
Pre-implant oral morphine dose mg/day	60 (20 - 120)	50 (40 - 240)	Z = -0.638	0.579
Morphine dose mg/day	4.625 (2.125 - 5.65)	1.612 (0.625 – 5.5)	Z = -2.205	0.028
Adjuvant intrathecal medication (Y/N)	4/1	5/5		0.580
Bupivacaine dose mg/day	3.190 (2.05 - 4.433)	2.050 (1.65 - 2.122)	Z = -1.715	0.111
Visual Analogue Scale	59 (0 - 69)	49.5 (10 - 64)	Z = -1.043	0.323
Oswestry Disability Questionnaire	54 (12 - 64)	55.85 (42 - 72)	Z = -0.677	0.529
Hospital Anxiety and Depression scale				
HAD anxiety	8 (2 - 16)	7.5 (1 - 12)	Z = -0.369	0.745
HAD depression	7 (2 - 11)	7.5 (2 - 15)	Z = -0.802	0.450
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	11.5 (0 - 31)	Z = -0.147	0.918
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.477	0.690
Catastrophising	7 (2 - 31)	22 (1 - 27)	Z = -0.147	0.911
Ignoring pain sensations	8 (3 - 21)	8 (0 - 28)	Z = -0.221	0.862
Praying or hoping	14 (2 - 26)	18.5 (0 - 30)	Z = -0.366	0.753
Coping self-statements	25 (15 - 30)	19 (2 - 32)	Z = -0.954	0.375
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.366	0.753
Control over pain	2 (1 - 5)	3 (1 - 4)	Z = -0.301	0.757
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -0.846	0.543
Cognitive coping and suppression	32 (18 - 70)	32.5 (6 - 83)	Z = -0.293	0.833
Helplessness	-7 (-14 - 10)	2 (-36 - 11)	Z = -0.806	0.458
Diverting attention and praying/hoping	26 (2 - 54)	31.5 (0 - 56)	Z = -0.440	0.698

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented p < 0.05

There were no statistically significant differences between the groups at baseline for age, gender, duration of therapy prior to study, adjuvant intrathecal medications, VAS, ODI, HAD scale and CSQ (Table 1). The intrathecal opioid dose administered at study entry was significantly higher in the control group (Mdn = 4.625) than in the intervention group (Mdn = 1.612), a chance finding, U = 7.00, p = 0.028, r = -0.57. A comparison of baseline scores between patients who completed the study and those that did not complete demonstrates non-

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significant differences for all the variables, including intrathecal dose administered at start of investigation (Table 2).

Table 2. Baseline characteristics of the patients according to completion of study

Characteristic	Complete (n = 8)	Incomplete (n = 7)	Test statistic	P
Age (years)	56.5 (45 - 68)	64 (53 - 66)	Z = -1.102	0.296
Gender (M/F)	6/2	2/5		0.132
Duration of therapy (months)	25 (15 - 88)	27 (12 - 180)	Z = -0.081	0.960
Pre-implant oral morphine dose mg/day	60 (20 - 120)	60 (40 - 240)	Z = -0.241	0.869
Morphine dose mg/day	3.065 (1.02 - 5.65)	1.6 (0.62 – 5.5)	Z = -1.273	0.232
Adjuvant intrathecal medication (Y/N)	5/3	4/3		1.000
Bupivacaine dose mg/day	2.5 (1.7 – 4.25)	2.085 (1.86-2.12)	Z = -0.735	0.556
Visual Analogue Scale	44.5 (0 - 69)	54 (23 - 64)	Z = -0.522	0.632
Oswestry Disability Index	53 (12 - 64)	57.7 (42 - 72)	Z = -1.222	0.244
Hospital Anxiety and Depression scale				
HAD anxiety	7 (2 - 16)	8 (1 - 12)	Z = -0.116	0.934
HAD depression	9 (2 - 15)	7 (2 - 12)	Z = -0.816	0.447
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	13 (0 - 31)	Z = -0.501	0.649
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.466	0.714
Catastrophising	22 (2 - 31)	15 (1 - 27)	Z = -0.575	0.608
Ignoring pain sensations	8 (0 - 21)	8 (0 - 28)	Z = -0.215	0.861
Praying or hoping	15 (2 - 30)	18.5 (0 - 25)	Z = -0.358	0.760
Coping self-statements	24 (13 - 30)	19 (2 - 32)	Z = -0.358	0.755
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.143	0.916
Control over pain	2 (1 - 5)	3.5 (2 - 4)	Z = -1.101	0.317
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -1.050	0.386
Cognitive coping and suppression	32 (12 - 70)	32.5 (6 - 83)	Z = -0.000	1.000
Helplessness	-5 (-14 - 11)	0 (-36 - 10)	Z = -0.215	0.868
Diverting attention and praying/hoping	27 (2 - 54)	31.5 (0 - 56)	Z = -0.287	0.809

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented p < 0.05

The VAS change between baseline and last observation was lower in the control group (Mdn = 11) than in the intervention group (Mdn = 30.5), although not statistically significant, Z = -1.839, p = 0.070, r = -0.47 (Table 3). There were no statistically significant differences between the randomised groups in the changes detected for ODI, HAD scale anxiety and depression and all items of CSQ between baseline score and final observation.

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Table 3. Changes between baseline and last observation

	Control group (n = 5)	Intervention group (n = 10)	Test statistic	P
VAS	11 (-4 - 40)	30.5 (2 - 77)	Z = -1.839	0.070
ODI	12 (4 - 18)	6 (-2 - 30)	Z = -1.070	0.311
HAD anxiety	1 (-6 - 3)	0.5 (-3 - 5)	Z = -0.523	0.653
HAD depression	0 (-1 - 3)	0 (-3 - 6)	Z = -0.074	0.959

Median (minimum-maximum); variables analysed using Mann-Whitney U test (Exact sig. (2-tailed))

Within group comparisons were also carried out (Table 4). Statistically significant differences for VAS were observed between baseline and last observation in the group randomised to have dose reduction (intervention) but not in the control group (p = 0.188). The VAS was significantly lower at baseline (*Mdn* = 49.5) than at last observation (*Mdn* = 77.5) for the intervention group, Z = -2.805, p = 0.002, r = -0.627 (Figure 2). The ODI scores at baseline (*Mdn* = 55.85) were significantly lower than at last observation (*Mdn* = 68.40) for the group allocated to have dose reduction, Z = -2.201, p = 0.027, r = 0.492. No statistically significant differences were observed for the ODI in the control group (p = 0.063). There were no statistically significant changes detected for HAD scale anxiety and depression and all items of CSQ in either randomised group between baseline score and final observation.

Table 4. Within group analysis for VAS and ODI

		VAS	ODI
Control group (n = 5)	Baseline	59 (0 - 69)	54 (12 - 64)
	Last observation	70 (40 - 83)	64 (30 - 74)
	Test statistic	Z = -1.625	Z = -2.032
	P	0.188	0.063
Intervention group (n = 10)	Baseline	49.5 (10 - 64)	55.85 (42 - 72)
	Last observation	77.5 (57 - 100)	68 (48 - 84)
	Test statistic	Z = -2.805	Z = -2.201
	P	0.002	0.027

Median (minimum-maximum); variables analysed using Wilcoxon test (Exact sig. (2-tailed))

The calculation of clinical changes based on the VAS scores indicated non-significant clinical changes in 10% of the patients in the dose reduction group (intervention), minimally clinically important changes (≥10% and <30%) were observed in 20% of the participants randomised to this group, moderately important increase in pain (≥30% and <50%) in 40% of the subjects and substantially important increase in pain (≥50%) in 30% of the patients. For the group where the

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morphine dose remained the same (control), non-significant changes were observed in 40% of the sample, minimally clinically important changes (≥10% and <30%) in 40% of the participants and one patient (20%) had a clinically substantial increase in pain.

(Insert Figure 2 here)

DISCUSSION

This randomised controlled trial of intrathecal opioid therapy in chronic non-malignant pain has demonstrated differences in pain relief between dose reduction and dose maintenance. It lends support to the efficacy of this therapy, which until now has not been subject to controlled trials.

A power analysis indicated that 24 patients would need to be included in the study to obtain a power of 0.8; however, due to high number of withdrawals, we undertook an interim analysis in which we found that the withdrawals were all in the dose reduction arm. The attrition rate of 70% in the group randomised to have reduction also indicates that the treatment seems to be effective. Statistically significant differences between the arms were observed and the study was stopped. Although not statistically significant, the VAS change between baseline and last observation was lower in the control group than in the reduction group. Within group VAS and ODI differences were statistically significant between baseline and last observation for the treatment arms with statistically significant greater pain and worsened disability in the dose reduction arm. Clinically important changes indicating an increase in pain intensity were observed in 90% of the patients randomised to dose reduction (intervention). These changes were moderately important (≥30% and <50%) in 40% of the patients and substantially important (≥50%) in 30% of the participants.

Significant differences between groups at enrolment were observed for morphine dose. The dose maintenance group (control) were found to have a significantly higher starting opioid dose. This mirrored the statistically insignificant trend towards longer duration of intrathecal therapy. It is possible that this group had greater levels of pain than the intervention group for the same dose of opioid and/or that with longer duration of therapy, the dose had increased with time, as a small increase in opioid dose may be necessary to maintain an adequate pain control and recent observations from our unit indicate that significant differences cease following year 3 of therapy suggesting stability.[12] When dose escalation occurs, it is usually due to tolerance, progress of the disease [34] or opioid induced hyperalgesia.[35]

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All subjects had stable levels of opioid delivery as evidenced by no change in delivered dose at recent refills before investigation and all reported analgesia with comparable pain scores (VAS). In using percentage dose reduction in this study, we anticipated overcoming a potential bias from this. Furthermore, no significant differences were observed at enrollment between those who completed the study and those who withdrew before completion, indicating that the initial opioid dose did not impact on drop-out rate. We had purposely chosen a small decrease of dose (20%) to avoid the patients suffering any withdrawal symptoms and none occurred. This parallels the experience of Rauck and colleagues in a study of opiate reduction within the context of investigating ziconotide.[36] In this study there was a 3 week weaning period prior to entering the trial and thus the weekly reduction in IT opioids would therefore be approximate to 30%. The weaning process was successful in 92.9% of the patients, only 14 dropped out due to inability to tolerate withdrawal, adverse events, noncompliance or patients request.

This study has recognised weaknesses of small sample size and being conducted in a single centre. The sample size was inferior to the 24 patients indicated by the a priori power analysis as the study was stopped when an interim analysis was conducted due to large number of drop-outs and revealed significant differences for withdrawals between groups. There was an imbalance in the number of patients in each group. The patients were randomised as a single block of 24, thus ensuring that in a sample of 24 there would be 12 in each group. Randomisation of smaller blocks would ensure that there were equal numbers in each group for smaller sample sizes as well (e.g. if we had used a block size of 6, we would have had equal numbers in each group after 6, 12, 18 and 24 patients had been randomised). With our single block of 24, the chance of getting a split as uneven as 10 and 5 after 15 patients was about 9%. This RCT was conducted in a single centre. Selection for therapy followed the national guidelines;[8] however, their interpretation may vary in clinical practice even within the same country in the psychosocial domains of pain. Dose titration strategies may differ across treatment centres. Different centres have reported average doses of 4.7 mg/day at an average of 3.4 years,[37] 7.42 mg/day at 29.14 months,[38] 9.6 mg/day at year 1 [39] and 12.2 mg/day at year 3.[40] This may lead to different levels of opioid delivery for which the sensitivity to dose reduction may differ.

The strengths of this study were not looking in the period following intrathecal drug delivery implantation because we considered that this period is confounded by need for dose titration

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and the non-specific psychological effects of a major intervention. In investigating patients with intrathecal delivery for a minimum of 12 months, we have been able to focus on evaluation of long term efficacy of intrathecal opioid therapy. To our knowledge this is the first randomised double-blind controlled study of this therapy in non-cancer pain. The findings of our randomised controlled trial suggest the efficacy of intrathecal morphine for the management of chronic non-cancer pain. Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction. In the light of these results, investigation of different populations and larger cohorts are recommended.

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Figure legends

Figure 1. Flow chart of patient participation

Figure 2. Individual visual analogue scale scores at baseline and final observation for control group (n=5) and reduction group (n=10).

ARTICLE SUMMARY

Article focus

- Recent systematic reviews were unable to find randomised controlled trials evaluating the effectiveness of long-term intrathecal drug delivery systems for the management of chronic non-cancer pain.

- We aimed to investigate if a small decrease in the intrathecal morphine dose leads to an increase in reported pain scores in chronic non-cancer pain patients undertaking long-term intrathecal morphine.

- The randomised controlled trial design would allow to investigate the long-term efficacy of intrathecal morphine delivery.

Key messages

- Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction.

- The findings of this study suggest the efficacy of intrathecal morphine delivery for the management of chronic non-cancer pain.

Strengths and limitations of this study

- To our knowledge, this is the first randomised controlled trial investigating the efficacy of intrathecal drug delivery systems for the management of chronic non-cancer pain.

- By investigating patients with intrathecal delivery for a minimum of 12 months this study is not confounded by need for dose titration and the non-specific psychological effects of a major intervention.

- Limitations of this study include small sample size and being conducted in a single centre.

Acknowledgments

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Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

JHR designed and was responsible for the conception of the trial. JHR, RVD, JLS, PN, GDK have made substantial contributions to (1) the acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

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Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain

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ABSTRACT

Objective

This study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity.

Design

Randomised, double blind, controlled, parallel group trial.

Setting

Department of Pain Management, Russells Hall Hospital, Dudley, United Kingdom.

Participants

Twenty-four non-cancer pain patients implanted with morphine reservoirs were assessed for eligibility.

Interventions

Participants were randomly allocated to one of two parallel groups in which one of the groups had no change in morphine dose and the other group had a small reduction (20%) in dosage every week during a 10-week follow-up.

Outcome

Primary outcomes were visual analogue scale (VAS) pain score change and withdrawal from study due to lack of efficacy.

Results

Nine of the patients assessed for eligibility declined to participate in the study. Fifteen patients were randomised to control (n=5) or intervention (n=10) and included in an intention-to-treat analysis. Due to worsening of pain, seven patients withdrew from the study prematurely. None knew prior to withdrawal which arm of the study they were in, but all turned out to be in the dose reduction arm. Calculation of drop-out rate between groups indicated a significant statistical difference (p=0.026) and recruitment was ceased. VAS change between baseline and last observation was smaller in the control group (Mdn=11) than in the intervention group (Mdn=30.5), although not statistically significant, Z=-1.839, p=0.070, r=-0.47. Within groups, VAS was significantly lower at baseline (Mdn=49.5) than at last observation (Mdn=77.5) for the reduction group, Z=-2.805, p=0.002, r=-0.627 but not for the control group (p=0.188).

Conclusion

This double blind RCT of chronic intrathecal morphine administration suggests effectiveness of this therapy for the management of chronic non-cancer pain. However, due to small number of patients completing the study (n=8) further studies are warranted.

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Trial registration

International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

INTRODUCTION

Opioid receptors were identified in the spinal cord in 1973.[1] Subsequent animal studies demonstrated that intrathecal opioids produce powerful and highly selective analgesia.[2] Intrathecal opioids exert their analgesic effect pre and post synaptically by reducing neurotransmitter release and by hyperpolarising the membranes of neurones in the dorsal horn, thus inhibiting pain transmission.[3]

The technique of intrathecal drug delivery is based on the principle that effective analgesia can be achieved by the action of some drugs at the dorsal horn and adequate concentrations cannot be achieved by systemic administration, or only by high systemic doses. Delivery of the drug by the intrathecal route is a means of achieving these enhanced therapeutic effects. The smaller doses needed for intrathecal administration also allow a reduction in side effects compared to systemic administration. Following the first clinical use of epidural [4] and intrathecal opioids,[5] Cousins used the expression 'selective spinal analgesia' to describe the phenomenon that spinally administered opioids could produce a specific analgesic effect with few motor, sensory or autonomic side effects.[6] It was subsequently demonstrated that the analgesic effect was, in the main, due to the uptake of the opioid directly into the spinal cord and cerebrospinal fluid.[3]

Key indications for intrathecal drug delivery systems are chronic pain unresponsive to curative medical or surgical measures and to more conservative palliative measures including systemic analgesics, physical therapies, psychological therapies, perineural injection procedures and nerve lesioning procedure. Pathologies for the pain are broad and only exclude psychogenic pains; they can be due to cancerous or non-malignant pathologies. Morphine is considered the 'gold standard' medication for intrathecal drug delivery systems because of its stability, receptor affinity and extensive experience of using the drug by this route.[7]

For chronic non-malignant pain it is strongly recommended that patients have a comprehensive psychological assessment [8] to: (i) assess possible concurrent psychopathology (e.g. severe affective disorder, body dysmorphia, procedural fears) that might impede successful implantation; and (ii) consider what additional individualised preparation might be advisable for the patient.[9] Cognitive behavioural therapy should not be excluded as a subsequent treatment

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option. It may ensure that the reduction in pain severity expected as a result of the ITDD system is capitalized upon by the development of reduced pain related behaviours and increased activity in a range of adaptive behaviours.

The first reservoir for intrathecal analgesic delivery was implanted in 1981,[10] and since then continuous intrathecal analgesia using opioids and other analgesics has become a recognized therapy for the management of severe and otherwise intractable chronic pain despite a lack of well-controlled studies. A three-year prospective study of intrathecal opioid treatment for chronic non-cancer pain showed that when patients with extremely severe pain problems are selected for intrathecal drug delivery, they are likely to improve with the therapy but their overall severity of pain and symptoms still remains high.[11] At least minimally clinical important changes in pain intensity were observed in 95% of participants in a recent study with a mean follow-up duration of 13 years.[12] Improvements were also observed in sensory and psychosocial outcomes.

Recent systematic reviews were unable to find randomised controlled trials (RCTs) evaluating the effectiveness of long-term intrathecal drug delivery systems (IDDS) for the management of chronic non-cancer pain.[13,14] Overall, the use of intrathecal opioid administration seems beneficial but the current available literature is too sparse to draw definite conclusions mainly due to the quality of the evidence. A systematic review of multiple well-designed RCTs is considered the highest level of evidence for the efficacy of a pain treatment, followed by a well-designed RCT of adequate size as the next best level of evidence.[15] To our knowledge there is only one such study of intrathecal opioids and that is confined to cancer pain.[16]

In the absence of strong supporting evidence for the use of intrathecal opioids for chronic non-cancer pain, the therapy must be balanced against its risks as procedure related complications have been reported to occur at a rate of 0.29 events per patient year and catheter related complications at a rate of 0.05 events per patient year.[17] Possible infections include meningitis, epidural abscess, pump pocket infection or pump reservoir infection. The rate of meningitis reported by studies ranged from 2.3% to 15.4% and for wound infections from 4.2% to 8.8%.[18] When considering only non-cancer pain studies, the percentage of patients with meningitis ranged from 0% to 4% and for wound infections, from 0% to 22%.[19] Furthermore, less common but serious events of permanent neurological injury can occur due to development of opioid associated granulomata. The incidence for this adverse event has been reported as 0.04% after one year, increasing to 1.15% after six years.[20] The management of the different

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adverse events is varied as some acute side-effects may resolve with time (e.g. nausea, vomiting, dizziness, or itching). Recommendations for aftercare, on-going care, prevention and management of potential complications and side-effects has been described.[8,18]

We had previously undertaken a prospective controlled study, of single dose morphine compared with saline in patients with chronic non-malignant pain and demonstrated spinal morphine to be efficacious in the short term for patients who respond to systemic morphine but in whom side effects have become intolerable.[21] The current study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity. Our primary outcome was visual analogue pain score change and withdrawal from study due to lack of efficacy.

METHODS

Study design and participants

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462). We conducted a single centre, double-blind, equal randomization [1:1], dose reduction, controlled, parallel group study. All subjects provided written informed consent. The original protocol anticipated using diamorphine, but between trial approval and trial commencement, practice changed to using morphine and the protocol was amended to reflect this.

Treatment strategies for the management of chronic pain start with the lowest risk and least invasive intervention and progress if a treatment is not effective. IDDS is a last-resort treatment to treat severe chronic pain because of their invasive nature, concerns about long-term opioid use, and the possible complications related to the procedure. IDDS is considered for use in patients with chronic non-cancer pain after more conventional treatments have failed (e.g. pharmacotherapy, transcutaneous electrical stimulation or in some cases spinal cord stimulation) and in those who respond to systemic opioids but the side effects have become intolerable. Patient suitability is also determined by a multidisciplinary team assessment that includes a clinical psychologist. A biopsychosocial history is performed, in which factors such as organic cause of pain, topography, duration of pain, pain intensity, coping strategies, social support, medico legal matters, history of anxiety and/or depression, previous treatments, and

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drug and/or alcohol abuse is taken into consideration. Where there is discrepancy across the clinical team of physician, physiotherapist, psychologist and specialist nurse, a case conference is set up to include the family physician, and other psychologists, physiotherapists and physicians not directly involved in intrathecal therapy.

Following multidisciplinary assessment all patients have an inpatient trial of intrathecal therapy prior to implantation. This is conducted by repeated bolus of morphine and saline in a single blind fashion.[21] Patients reporting greater than 50% relief with morphine and less with saline are selected for IDDS. Chronic dosing is extrapolated and titrated at refills (approximately two per month initially). A small increase in opioid dose may be necessary to maintain an adequate pain control. Recent observations indicate that significant differences cease following year 3 of therapy suggesting stability.[12] Additional intrathecal drugs were added if level of analgesia is inadequate as per polyanalgesic consensus conference algorithm.[22] Adjuvant intrathecal medication such as bupivacaine may contribute to achieve better pain control and to maintain low intrathecal morphine doses in cancer [23] and non-cancer patients.[24]

Eligible participants were adults aged 18 or over with implanted intrathecal reservoirs of programmable type (Synchromed, Medtronic Ltd) receiving intrathecal morphine for non-cancer pain and having had infusion for ≥ 12 months. Patients had reported a stable level of analgesia with the pump, based upon their attendance for pump refills at which dose did not change and they reported analgesia. In view of the need for weekly attendance during the study only those patients living within a short time journey from the hospital, with access to transport and limited co-morbidities were considered.

The pain nurse approached eligible patients for consent and patients were randomly assigned by computer generated randomization (PN) to one of two parallel groups in which one of the groups had no change in the morphine dose (control group) and the other group had a small reduction (20%) in the preceding week dose every week during participation in the study (intervention group). The allocation sequence was received in sequentially numbered, opaque and sealed envelopes to ensure that the sequence was concealed. Patients were unaware as to which group they were in, as the dose alteration or no change was conducted by telemetry with the screen not visible to the patient. The telemetry was conducted by a physician (JHR) who was the only investigator aware of the allocation. Pain scores and other outcome measures were collected by a researcher (RVD) blinded to the allocation of the patients.

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Outcome measures

Primary outcome measures were visual analogue scale (VAS) [25] score for pain and withdrawal from study. Secondary outcome measures were functional and psychological measures based on Oswestry Disability Index (ODI),[26] Hospital Anxiety and Depression scale (HAD)[27] and Coping Strategies Questionnaire (CSQ).[28] Subjects were evaluated at baseline and each week during participation in the study. VAS and ODI were collected on a weekly basis. HAD and CSQ were collected fortnightly.

Patients were asked to rate their average pain intensity during the previous week using a VAS. The VAS consists of a 100 mm straight line with anchors at its ends labelled as no pain and worst pain imaginable. The VAS is a recognised method for the assessment in variation of pain intensity.[25,29] Clinically important changes were classified in accordance with a consensus statement that established a 10-20% decrease as minimally important, ≥ 30% as moderately important and ≥ 50% as a substantial change.[30]

The ODI is used to assess the level of pain interference with various activities of daily living. The ODI is a valid measure of condition-specific disability.[31] The ODI consists of 10 items/activities with 6 levels (range 0-5). Scoring of this questionnaire was calculated as recommended by Fairbank and Pynsent.[31]

The HAD scale is a self-report rating scale of 14 items with 4 levels (range 0-3). This scale is used to screen for anxiety and depression (7 intermingled items for each subscale). The total score for each subscale is the sum of the respective seven items (ranging from 0–21). The HAD scale is considered a valid instrument for detecting states of anxiety and depression.[32]

The CSQ is a self-report instrument to assess active and passive coping skills of chronic pain patients.[33] The CSQ includes cognitive coping strategies (diverting attention, reinterpreting pain sensation, catastrophising, ignoring pain sensations, praying or hoping, coping self-statements), behavioural coping strategies (increasing activity level), and effectiveness ratings (control over pain, ability to decrease pain). Scores of these subscales result in 3 factors that account for 68% of the variance in questionnaire responses (cognitive coping and suppression, helplessness, diverting attention and praying). This questionnaire is a valid and reliable tool for chronic pain patient assessment.[28]

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Data analysis

An *a priori* power analysis based on previous open study data of reduction in VAS for pain with intrathecal therapy [21] computed a sample size of 24 (12 per group) would provide 80% power at the 5% significance level to detect a difference in the means of 1.2 standard deviations (unpaired t test) or a difference between the two proportions 20% and 80% (Fisher's Exact Test). The power analysis was based on a study which compared one group receiving morphine with one group receiving placebo (saline). The difference in means in the pilot study (5.1-0.91 = 4.19) was not used as the basis for the power calculation as the difference in the pilot study was likely to be larger than the difference observed in the current study where both groups received morphine. A difference in the means of 1.2 standard deviations was considered as a realistic estimate since we allowed for the effect to be much smaller than that observed in the pilot study (2.6 standard deviations if the standard deviations of 1.3 and 1.9 are pooled). Imputation methods were not used since the drop-out rate in the group randomised to have intrathecal dose reduction was 70%. This high drop-out percentage rate would bias the results regardless of the imputation technique employed. Therefore, we followed an intention-to-treat protocol; all subjects were included in the analysis and this was limited to within and between-group comparisons of baseline and final observation scores.

Kolmogorov-Smirnov test was performed to test normality of numerical data. The majority of the numerical data was not normally distributed and attempts to transform the data were unsuccessful. Therefore, differences between patient baseline characteristics were performed using the Mann-Whitney U test. Differences between baseline and last observation scores were evaluated using Wilcoxon Signed Ranks test. Categorical variables were investigated using Fisher's exact test. Data is reported as median (minimum-maximum). Statistical significance was judged at 5% level. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0, SPSS Inc., Chicago, IL, USA).

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RESULTS

Between 2006 and 2011, 24 patients were assessed for eligibility, nine declined to participate. Following inclusion in the study of 15 patients, it was observed that a high rate of patients withdrew from the research (Figure 1). Because of the large number of withdrawals, a first interim analysis was undertaken just beyond half way point which revealed that the withdrawals were all from the group randomised to have dose reduction. One subject left the study following week 1, three patients withdrew after week 2, two participants after week 5 and one patient after week 7. The intrathecal opioid dose in the patients that withdrew from the study was reduced from a median of 1.6 mg/day (0.625 – 5.5) to 1.15 mg/day (0.4 – 2.8) which corresponds to a decrease of 36% (20 - 79) in the intrathecal opioid dose. The reason for drop-out from the study was related with worsening of pain for all the participants. Calculation of drop-out rate between the groups indicated a significant statistical difference (p = 0.026). Recruitment ceased at that moment.

(Insert Figure 1/flow diagram here)

The patients recruited comprised 8 men (53.3%) and 7 women (46.7%) with a median age at the moment of enrolment in the study of 58 years (45-68). The median duration of IDDS therapy prior to participation in this study was 26 months (12-180). The pain syndrome was mechanical nociceptive caused by degenerative low back pain in 5 (33.3%) of the participants; visceral nociceptive due to post surgery abdominal pain in 1 (6.7%) patient and mixed nociceptive-neuropathic following failed back surgery syndrome in 9 (60%) subjects. The 5 patients in the control group comprised 2 with mechanical back pain and 3 with failed back surgery syndrome; the 10 in the intervention group comprised 3 with mechanical back pain, 6 with failed back surgery syndrome and 1 with post-surgery abdominal pain. All patients had been on systemic opioids prior to pump implantation and thereafter only took opioids intrathecally. The preparations differed and the equivalent oral morphine dose prior to implant ranged from 20 to 240mg morphine equivalent per day (Table 1 and 2).

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Table 1. Baseline characteristics of the patients according to randomization group

Characteristic	Control group (n = 5)	Intervention group (n = 10)	Test statistic	P
Age (years)	55 (45 - 59)	64 (52 - 68)	Z = -1.719	0.095
Gender (M/F)	4/1	4/6		0.282
Duration of therapy (months)	66 (22 - 88)	20.5 (12 - 180)	Z = -1.191	0.265
Pre-implant oral morphine dose mg/day	60 (20 - 120)	50 (40 - 240)	Z = -0.638	0.579
Morphine dose mg/day	4.625 (2.125 - 5.65)	1.612 (0.625 – 5.5)	Z = -2.205	0.028
Adjuvant intrathecal medication (Y/N)	4/1	5/5		0.580
Bupivacaine dose mg/day	3.190 (2.05 - 4.433)	2.050 (1.65 - 2.122)	Z = -1.715	0.111
Visual Analogue Scale	59 (0 - 69)	49.5 (10 - 64)	Z = -1.043	0.323
Oswestry Disability Questionnaire	54 (12 - 64)	55.85 (42 - 72)	Z = -0.677	0.529
Hospital Anxiety and Depression scale				
HAD anxiety	8 (2 - 16)	7.5 (1 - 12)	Z = -0.369	0.745
HAD depression	7 (2 - 11)	7.5 (2 - 15)	Z = -0.802	0.450
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	11.5 (0 - 31)	Z = -0.147	0.918
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.477	0.690
Catastrophising	7 (2 - 31)	22 (1 - 27)	Z = -0.147	0.911
Ignoring pain sensations	8 (3 - 21)	8 (0 - 28)	Z = -0.221	0.862
Praying or hoping	14 (2 - 26)	18.5 (0 - 30)	Z = -0.366	0.753
Coping self-statements	25 (15 - 30)	19 (2 - 32)	Z = -0.954	0.375
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.366	0.753
Control over pain	2 (1 - 5)	3 (1 - 4)	Z = -0.301	0.757
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -0.846	0.543
Cognitive coping and suppression	32 (18 - 70)	32.5 (6 - 83)	Z = -0.293	0.833
Helplessness	-7 (-14 - 10)	2 (-36 - 11)	Z = -0.806	0.458
Diverting attention and praying/hoping	26 (2 - 54)	31.5 (0 - 56)	Z = -0.440	0.698

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented *p* < 0.05

There were no statistically significant differences between the groups at baseline for age, gender, duration of therapy prior to study, adjuvant intrathecal medications, VAS, ODI, HAD scale and CSQ (Table 1). The intrathecal opioid dose administered at study entry was significantly higher in the control group (*Mdn* = 4.625) than in the intervention group (*Mdn* = 1.612), a chance finding, *U* = 7.00, *p* = 0.028, *r* = -0.57. A comparison of baseline scores between patients who completed the study and those that did not complete demonstrates non-

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significant differences for all the variables, including intrathecal dose administered at start of investigation (Table 2).

Table 2. Baseline characteristics of the patients according to completion of study

Characteristic	Complete (n = 8)	Incomplete (n = 7)	Test statistic	P
Age (years)	56.5 (45 - 68)	64 (53 - 66)	$Z = -1.102$	0.296
Gender (M/F)	6/2	2/5		0.132
Duration of therapy (months)	25 (15 - 88)	27 (12 - 180)	$Z = -0.081$	0.960
Pre-implant oral morphine dose mg/day	60 (20 - 120)	60 (40 - 240)	$Z = -0.241$	0.869
Morphine dose mg/day	3.065 (1.02 - 5.65)	1.6 (0.62 – 5.5)	$Z = -1.273$	0.232
Adjuvant intrathecal medication (Y/N)	5/3	4/3		1.000
Bupivacaine dose mg/day	2.5 (1.7 – 4.25)	2.085 (1.86-2.12)	$Z = -0.735$	0.556
Visual Analogue Scale	44.5 (0 - 69)	54 (23 - 64)	$Z = -0.522$	0.632
Oswestry Disability Index	53 (12 - 64)	57.7 (42 - 72)	$Z = -1.222$	0.244
Hospital Anxiety and Depression scale				
HAD anxiety	7 (2 - 16)	8 (1 - 12)	$Z = -0.116$	0.934
HAD depression	9 (2 - 15)	7 (2 - 12)	$Z = -0.816$	0.447
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	13 (0 - 31)	$Z = -0.501$	0.649
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	$Z = -0.466$	0.714
Catastrophising	22 (2 - 31)	15 (1 - 27)	$Z = -0.575$	0.608
Ignoring pain sensations	8 (0 - 21)	8 (0 - 28)	$Z = -0.215$	0.861
Praying or hoping	15 (2 - 30)	18.5 (0 - 25)	$Z = -0.358$	0.760
Coping self-statements	24 (13 - 30)	19 (2 - 32)	$Z = -0.358$	0.755
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	$Z = -0.143$	0.916
Control over pain	2 (1 - 5)	3.5 (2 - 4)	$Z = -1.101$	0.317
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	$Z = -1.050$	0.386
Cognitive coping and suppression	32 (12 - 70)	32.5 (6 - 83)	$Z = -0.000$	1.000
Helplessness	-5 (-14 - 11)	0 (-36 - 10)	$Z = -0.215$	0.868
Diverting attention and praying/hoping	27 (2 - 54)	31.5 (0 - 56)	$Z = -0.287$	0.809

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented $p < 0.05$

The VAS change between baseline and last observation was lower in the control group (Mdn = 11) than in the intervention group (Mdn = 30.5), although not statistically significant, $Z = -1.839$, $p = 0.070$, $r = -0.47$ (Table 3). There were no statistically significant differences between the randomised groups in the changes detected for ODI, HAD scale anxiety and depression and all items of CSQ between baseline score and final observation.

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Table 3. Changes between baseline and last observation

	Control group (n = 5)	Intervention group (n = 10)	Test statistic	*P*
VAS	11 (-4 - 40)	30.5 (2 - 77)	*Z* = -1.839	0.070
ODI	12 (4 - 18)	6 (-2 - 30)	*Z* = -1.070	0.311
HAD anxiety	1 (-6 - 3)	0.5 (-3 - 5)	*Z* = -0.523	0.653
HAD depression	0 (-1 - 3)	0 (-3 - 6)	*Z* = -0.074	0.959

Median (minimum-maximum); variables analysed using Mann-Whitney U test (Exact sig. (2-tailed))

Within group comparisons were also carried out (Table 4). Statistically significant differences for VAS were observed between baseline and last observation in the group randomised to have dose reduction (intervention) but not in the control group (*p* = 0.188). The VAS was significantly lower at baseline (*Mdn* = 49.5) than at last observation (*Mdn* = 77.5) for the intervention group, *Z* = -2.805, *p* = 0.002, *r* = -0.627 (Figure 2). The ODI scores at baseline (*Mdn* = 55.85) were significantly lower than at last observation (*Mdn* = 68.40) for the group allocated to have dose reduction, *Z* = -2.201, *p* = 0.027, *r* = 0.492. No statistically significant differences were observed for the ODI in the control group (*p* = 0.063). There were no statistically significant changes detected for HAD scale anxiety and depression and all items of CSQ in either randomised group between baseline score and final observation.

Table 4. Within group analysis for VAS and ODI

		VAS	ODI
Control group (n = 5)	Baseline	59 (0 - 69)	54 (12 - 64)
	Last observation	70 (40 - 83)	64 (30 - 74)
	Test statistic	*Z* = -1.625	*Z* = -2.032
	P	0.188	0.063
Intervention group (n = 10)	Baseline	49.5 (10 - 64)	55.85 (42 - 72)
	Last observation	77.5 (57 - 100)	68 (48 - 84)
	Test statistic	*Z* = -2.805	*Z* = -2.201
	P	0.002	0.027

Median (minimum-maximum); variables analysed using Wilcoxon test (Exact sig. (2-tailed))

The calculation of clinical changes based on the VAS scores indicated non-significant clinical changes in 10% of the patients in the dose reduction group (intervention), minimally clinically important changes (≥10% and <30%) were observed in 20% of the participants randomised to this group, moderately important increase in pain (≥30% and <50%) in 40% of the subjects and substantially important increase in pain (≥50%) in 30% of the patients. For the group where the

morphine dose remained the same (control), non-significant changes were observed in 40% of the sample, minimally clinically important changes (≥10% and <30%) in 40% of the participants and one patient (20%) had a clinically substantial increase in pain.

(Insert Figure 2 here)

DISCUSSION

This randomised controlled trial of intrathecal opioid therapy in chronic non-malignant pain has demonstrated differences in pain relief between dose reduction and dose maintenance. It lends support to the efficacy of this therapy, which until now has not been subject to controlled trials.

A power analysis indicated that 24 patients would need to be included in the study to obtain a power of 0.8; however, due to high number of withdrawals, we undertook an interim analysis in which we found that the withdrawals were all in the dose reduction arm. The attrition rate of 70% in the group randomised to have reduction also indicates that the treatment seems to be effective. Statistically significant differences between the arms were observed and the study was stopped. Although not statistically significant, the VAS change between baseline and last observation was lower in the control group than in the reduction group. Within group VAS and ODI differences were statistically significant between baseline and last observation for the treatment arms with statistically significant greater pain and worsened disability in the dose reduction arm. Clinically important changes indicating an increase in pain intensity were observed in 90% of the patients randomised to dose reduction (intervention). These changes were moderately important (≥30% and <50%) in 40% of the patients and substantially important (≥50%) in 30% of the participants.

Significant differences between groups at enrolment were observed for morphine dose. The dose maintenance group (control) were found to have a significantly higher starting opioid dose. This mirrored the statistically insignificant trend towards longer duration of intrathecal therapy. It is possible that this group had greater levels of pain than the intervention group for the same dose of opioid and/or that with longer duration of therapy, the dose had increased with time, as a small increase in opioid dose may be necessary to maintain an adequate pain control and recent observations from our unit indicate that significant differences cease following year 3 of therapy suggesting stability.[12] When dose escalation occurs, it is usually due to tolerance, progress of the disease [34] or opioid induced hyperalgesia.[35]

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All subjects had stable levels of opioid delivery as evidenced by no change in delivered dose at recent refills before investigation and all reported analgesia with comparable pain scores (VAS). In using percentage dose reduction in this study, we anticipated overcoming a potential bias from this. Furthermore, no significant differences were observed at enrollment between those who completed the study and those who withdrew before completion, indicating that the initial opioid dose did not impact on drop-out rate. We had purposely chosen a small decrease of dose (20%) to avoid the patients suffering any withdrawal symptoms and none occurred. This parallels the experience of Rauck and colleagues in a study of opiate reduction within the context of investigating ziconotide.[36] In this study there was a 3 week weaning period prior to entering the trial and thus the weekly reduction in IT opioids would therefore be approximate to 30%. The weaning process was successful in 92.9% of the patients, only 14 dropped out due to inability to tolerate withdrawal, adverse events, noncompliance or patients request.

This study has recognised weaknesses of small sample size and being conducted in a single centre. The sample size was inferior to the 24 patients indicated by the a priori power analysis as the study was stopped when an interim analysis was conducted due to large number of drop-outs and revealed significant differences for withdrawals between groups. There was an imbalance in the number of patients in each group. The patients were randomised as a single block of 24, thus ensuring that in a sample of 24 there would be 12 in each group. Randomisation of smaller blocks would ensure that there were equal numbers in each group for smaller sample sizes as well (e.g. if we had used a block size of 6, we would have had equal numbers in each group after 6, 12, 18 and 24 patients had been randomised). With our single block of 24, the chance of getting a split as uneven as 10 and 5 after 15 patients was about 9%. This RCT was conducted in a single centre. Selection for therapy followed the national guidelines;[8] however, their interpretation may vary in clinical practice even within the same country in the psychosocial domains of pain. Dose titration strategies may differ across treatment centres. Different centres have reported average doses of 4.7 mg/day at an average of 3.4 years,[37] 7.42 mg/day at 29.14 months,[38] 9.6 mg/day at year 1 [39] and 12.2 mg/day at year 3.[40] This may lead to different levels of opioid delivery for which the sensitivity to dose reduction may differ.

The strengths of this study were not looking in the period following intrathecal drug delivery implantation because we considered that this period is confounded by need for dose titration

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and the non-specific psychological effects of a major intervention. In investigating patients with intrathecal delivery for a minimum of 12 months, we have been able to focus on evaluation of long term efficacy of intrathecal opioid therapy. To our knowledge this is the first randomised double-blind controlled study of this therapy in non-cancer pain. The findings of our randomised controlled trial suggest the efficacy of intrathecal morphine for the management of chronic non-cancer pain. Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction. In the light of these results, investigation of different populations and larger cohorts are recommended.

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Figure legends

Figure 1. Flow chart of patient participation

Figure 2. Individual visual analogue scale scores at baseline and final observation for control group (n=5) and reduction group (n=10).

ARTICLE SUMMARY

Article focus

- Recent systematic reviews were unable to find randomised controlled trials evaluating the effectiveness of long-term intrathecal drug delivery systems for the management of chronic non-cancer pain.

- We aimed to investigate if a small decrease in the intrathecal morphine dose leads to an increase in reported pain scores in chronic non-cancer pain patients undertaking long-term intrathecal morphine.

- The randomised controlled trial design would allow to investigate the long-term efficacy of intrathecal morphine delivery.

Key messages

- Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction.

- The findings of this study suggest the efficacy of intrathecal morphine delivery for the management of chronic non-cancer pain.

Strengths and limitations of this study

- To our knowledge, this is the first randomised controlled trial investigating the efficacy of intrathecal drug delivery systems for the management of chronic non-cancer pain.

- By investigating patients with intrathecal delivery for a minimum of 12 months this study is not confounded by need for dose titration and the non-specific psychological effects of a major intervention.

- Limitations of this study include small sample size and being conducted in a single centre.

Acknowledgments

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Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

JHR designed and was responsible for the conception of the trial. JHR, RVD, JLS, PN, GDK have made substantial contributions to (1) the acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

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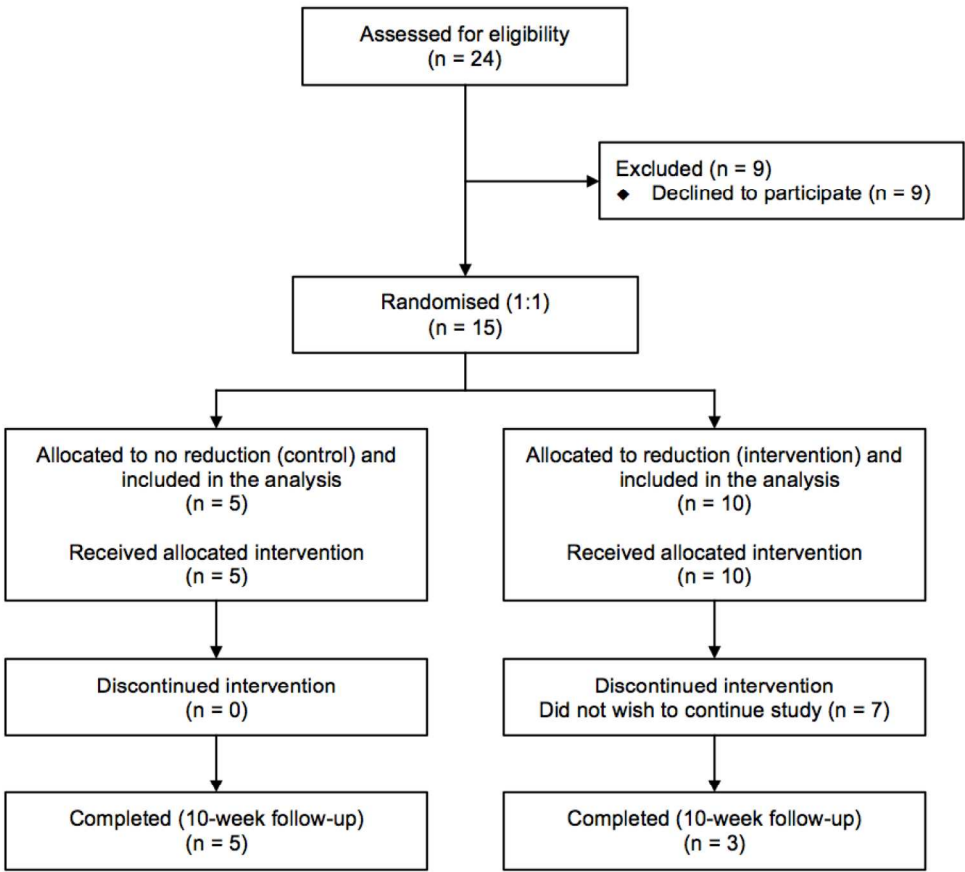
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                              │───────▶│ Excluded (n = 9)                      │
                              │        │  ◆ Declined to participate (n = 9)    │
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│                               │  │                               │
│ Received allocated intervention│  │ Received allocated intervention│
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│ Discontinued intervention     │  │ Discontinued intervention     │
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Figure 1. Flow chart of patient participation
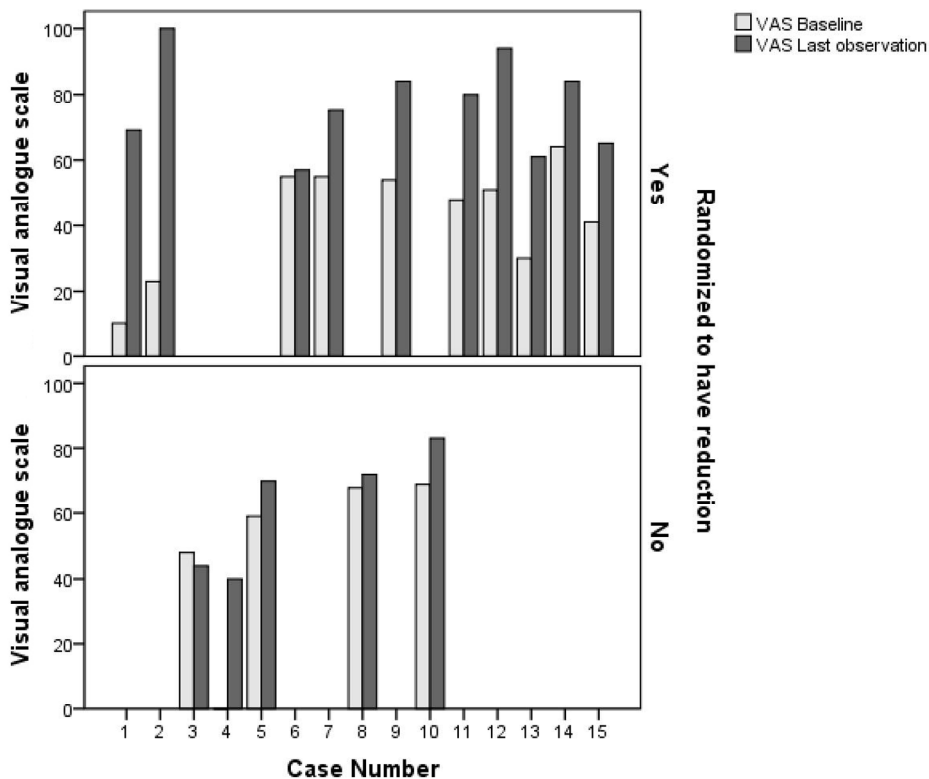331x295mm (300 x 300 DPI)

Figure 2. Individual visual analogue scale scores at baseline and final observation for control group (n=5) and reduction group (n=10)
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Birmingham and The Black Country **NHS**
Health Authority

Dudley Local Research Ethics Committee   12 Bull Street
Chair: Chris Spencer-Jones   Dudley
E-mail: chris.spencer-jones@dudley.nhs.uk   West Midlands
Administrator: Tracey Hartle   DY1 2DD
Direct Dial: 01384 366033
E-mail: tracey.hartle@dudley.nhs.uk   Tel: 01384 239376
                                                                Fax: 01384 455068

REC/38/02/JUN   Please quote this number on all correspondence

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23 July 2002

Dr J Raphael
Consultant in Pain Management
Russells Hall Hospital
DUDLEY
West Midlands
DY1 2HQ

Dear Dr Raphael

**Research Protocol: REC/38/02/JUN; Randomised controlled trial of intrathecal
diamorphine in the treatment of chronic non-malignant pain**

The Dudley REC reviewed your application on Friday 21 June 2002. The documents
reviewed were as follows:

- **Application Form (No Version Dated: 04/04/02)**
- **Patient information sheet and consent form (No Version No Date)**
- **Questionnaire (No Version No Date)**

The members of the Committee present agreed there is no objection on ethical grounds to
the proposed study. I am, therefore, happy to give you the favourable opinion of the
committee on the understanding that you will follow the conditions set out below:

Conditions

- You do not recruit any research subjects within a research site unless favourable opinion
  has been obtained from the relevant REC.

- You do not undertake this research in an NHS organisation until the relevant NHS
  management approval has been gained as set out in the Framework for Research
  Governance in Health and Social Care.

Minicom: (Text Phone Users) 01384 243187
DX: 709411 Dudley 5

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REC/35/02/JUN

- You do not deviate from, or make changes to, the protocol without prior written approval of the REC, except where this is necessary to eliminate immediate hazards to research participants or when the change involves only logistical or administrative aspects of the research. In such cases the REC should be informed within seven days of the implementation of the change.

- You complete and return the standard progress report form to the REC one-year from the date on this letter and thereafter on an annual basis. This form should also be used to notify the REC when your research is completed and in this case should be sent to this REC within three months of completion.

- If you decided to terminate this research prematurely you send a report to this REC within 15 days, indicating the reason for the early termination.

- You advise the REC of any unusual or unexpected results that raise questions about the safety of the research.

- Note that the LREC approval is necessary but not sufficient for you to undertake this research project within your local NHS organisation and you will require separate approval from your organisation's Research and Development Directorate/ management in accordance with the research governance framework. Care should also be taken to ensure with the NHS organisation that local indemnity arrangements are adequate.

Any comments the REC wished to make are contained in the attached REC Response Form. The project must be started within three years of the date on this letter.

Yours sincerely

Dr Chris Spencer-Jones
CHAIR

cc   Mrs M Marriott, R & D Department

RESEARCH ETHICS COMMITTEE
RESPONSE FORM

DETAILS OF APPLICANT:

1.   **Name and address of Principal Researcher:** Dr Jon Raphael, Consultant in
Pain Management, Russells Hall Hospital, Dudley, West Midlands

2.   **Title of project:** Randomised controlled trial of intrathecal diamorphine in the
treatment of chronic non-malignant pain

3.   **Name and address of Sponsor:**

DETAILS OF REC:

4.   **Name and address of REC:** Dudley REC, 12 Bull St, DUDLEY, West Midlands

5.   **REC Reference Number:** REC/38/02/JUN

**Listed below is a complete record of the review undertaken by REC with the decisions
made, dates of decisions and the requirements at each stage of the review:**

21/06/02

- *It was agreed that the design of this research application was sound and should
provide useful information. There was a question of the practicalities of using
diamorphine which is unstable and can be made up locally vs morphine that is
stable and can be prepared in sterile conditions. The committee asked Dr Raphael
to look into past infection rates using pumps and if there is a case for using sterile
preparations. Any risk should be discussed with the Trust's Clinical Governance
Department. Should there be a case for using morphine Dr Raphael should liaise
with Ron Pate*

THE FINAL DOCUMENTS AND ARRANGEMENTS APPROVED BY THE REC

The following items have been approved by the Dudley REC:

Protocol [No Version Dated: 04/04/02]
Subject information sheet [No Version No Date]
Subject consent form [No Version No Date]
Subject questionnaire [No Version No Date]

Date of approval: **June 21 2002**

Signature of Chair/Administrator: Date:

Name *(please print)*:   DR CHRIS SPENCER JONES

DUDLEY PAIN MANAGEMENT SERVICE

Jon Raphael MD MSc (Pain)
Consultant in Pain Medicine

Secretary: **Miss Julie Hackett**
Tel No: **01384 244809**
Fax No: **01384 244808**
Helpline: **01384 244735**
Email: <u>Julie.hackett@dgoh.nhs.uk</u>

JR/JH

27 January 2005

Dr J Neilson
Chairman
Research Ethics Committee
Haematology Department
Russells Hall Hospital

Dear Jeff

REC/38/02/JUN. RANDOMISED CONTROLLED TRIAL OF
INTRATHECAL DIAMORPHINE IN THE TREATMENT OF CHRONIC
NON MALIGNANT PAIN

In the middle of 2004 there was a directive from the Medical Devices Agency that
recommended Diamorphine no longer be used in intrathecal programmable pumps
because of a few reports of mechanical pump failure. It was thought that this was
related to the mono acetate metabolite of Diamorphine. Accordingly we are following
the recommendations of the Pain Society and all new implanted pumps are now filled
with Morphine and we are in the process of converting the existing pumps from
Diamorphine to Morphine. As you will appreciate since April 2004 we have not
recruited anybody to this study. We would, however, like to continue with this
research in respect of intrathecal Morphine as opposed to Diamorphine. Since
Diamorphine very rapidly breaks down to Morphine and when administered
intrathecally they are equivalent in dose (as shown in publication with Mourad Labib) we
would like to continue with the same protocol except but substituting the word
Diamorphine for Morphine throughout. The design of the study is a percentage dose
reduction protocol, the reported efficacy and side effects of intrathecal Morphine are
same as Diamorphine and therefore, we do not require to change the protocol in other
respect. I look forward to hearing from you.

With kind regards,
Yours sincerely

dictated but not signed

Jon Raphael MD MSc (Pain)
Consultant in Pain Medicine

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DESCRIPTION OF RESEARCH PROJECT FOR SUBMISSION TO THE DUDLEY LOCAL
RESEARCH ETHICS COMMITTEE

NOTE: ALL QUESTIONS MUST BE ANSWERED BY THE PERSON ACTUALLY UNDERTAKING
            THE RESEARCH.
            ANSWERS MUST BE TYPEWRITTEN. ANY FORMS NOT COMPLETED IN TYPE
            WILL BE RETURNED

1   Name(s) of Responsible Investigator(s):-

Jointly_
Jon Raphael, Consultant in Pain Management, Dudley GOH
David Booth, Professor of Psychology, Univ of Birmingham
George Kitas, Consultant Rheumatologist, Dudley GOH

2   Please advise the number of other trials/studies in which the local investigator
                    a) is currently involved?
                            5

                    b) has been involved in the last six months?
                            as above

2a   Title of Project:-

Randomised controlled trial of intrathecal diamorphine in the treatment of chronic non-malignant pain

2b   Clinical Trial Certificate Reference or Exemption Certificate Reference:-

            N/A

3a   Objective (i.e. hypothesis which it is intended to test):-

1. Intrathecal opioids are useful in the treatment of severe chronic non-
malignant pain

2. Therapeutic efficacy is dose-dependent

3. Gradual reduction of intrathecal opioid dose is safe

-1 -

3b What practical benefit do you envisage from a successful completion of this project?

Production of evidence of good scientific quality that this therapeutic approach is useful (or not) in severe chronic non-malignant pain

Identification of the most appropriate diamorphine dose that should be used for treatment, with the minimum potential for side effects

4 Design of the Study (describe briefly):-

Patients will be recruited from those already with an implanted intrathecal drug delivery system providing diamorphine for chronic non-malignant pain.

All patients meeting above criteria will be approached for recruitment and those who consent to enter this study will be randomised by random numbers generator into one of two groups:

Group 1 will have the dose of diamorphine reduced every week by 20% of the preceeding weeks dose for 10 weeks.

week	dose (as percentage of starting dose)
0	100%
1	80
2	64
3	51
4	41
5	33
6	25.5
7	20.5
8	16.5
9	13
10	10

Group 2 has no change in dose at these weekly visits.
The above changes are made by computer telemetry to which patient is blinded.

Measurements will be made at these weekly visits as follows:
1. Pain will be measured using Visual Analogue Scale (VAS)
2. Function will be measured by the Ostwestry Disability Score (ODS)
3. Psychological parameters will be measured by the Hospital Anxiety Depression Score (HAD) and the Pain Coping Strategies Questionnaire (PCSQ)
4. Sociological parameters will be measured by the Short Form-36 Questionnaire (SF-36)
5. An overall assessment of change will be measured by the Global Impression of Change (GIC).

Endpoint will be withdrawal due to inefficacy or withdrawal due to side effects

-2-

5a Scientific background: give a brief account:-

Chronic non-malignant pain has enormous social and economic consequences (CSAG, 1994). A wide variety of treatments are used including drugs, physical therapies, operations and psychological treatments. Although they appear to help some patients and many have been subjected to studies that support their benefit, there remain a number of patients who continue despite this to have severe chronic and disabling pain.

The discovery of opioid receptors in the spinal cord led to the rationale use of intrathecal opioids for pain relief (Wang, 1979). This was initially used in those patients with cancer. With the development of implantable, programmable, continuous drug delivery systems in the 1980s, the use of intraspinal opioids was extended to non-cancer pain.

Published data on the outcome of this therapy is limited to retrospective studies from the USA (Paice, 1996), Europe (Winkelmuller, 1996) and the UK (Raphael, 2000). Nevertheless , these studies consistently support its benefits in alleviating pain and improving quality of life as reported by the National Institute of Clinical Excellence (NICE) (Williams, 2001). It also appears to be cost effective since less drugs and other treatments are needed after spinal pump implantation (Mueller-Schwefe, 1999).

The NICE document expressed the need for comparator studies to provide more robust data and I am in the process of designing a multi-centre prospective randomised placebo controlled trial to address this in new patients in liason with the Birmingham Clinical Trials Unit. However, a lot can be learnt from patients already receiving this therapy. These cannot be randomised in a placebo controlled trial because opioid withdrawal would lead to unacceptable side effects. They can be randomised to a dose-ranging trial as described above which will produce information about the efficacy (or not) of this therapy and the optimum dose.

5b Has the investigation been done previously with human subject?

No

5c If so, why repeat it?

6a Subjects:How many are needed?

Power calculations have been based on previous open study with pain as primary outcome. 24 patients are required in total (12 per group) to provide 80% power at the 5% significance level

and how selected?

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Patients receiving intrathecal diamorphine for chronic non-malignant pain by implanted computerised drug delivery system. As the regional centre for this therapy we have sufficient patients attending for follow up to acheive the required sample size.

6b   Are the patients included in this study involved in any other research investigation at the   present time?

No

6c   Controls: how many are needed?

12 (described above)

6d   What is the primary end point?
Pain relief by VAS
Withdrawal from protocol due to inefficacy

7a   Have you taken any statistical advice on the numbers required for your study to give   scientific
validity
                    YES

7b   If YES from whom was the advice obtained?

D. Booth, Professor of Health Psychology, Univ of Birmingham

7c   If NO why not?

N/A

8a   Substances to be given to the subjects (special diets, drugs, isotope tracers etc):-

STATE ROUTE OF ADMINISTRATION, AMOUNT & EFFECTS ANTICIPATED:

N/A

8b   Who will cover the costs of these substances?

-4 -

8c   How will they be stored and issued?

9a   Samples to be taken from the subjects (venepuncture, arterial, urine, biopsy etc):

         STATE TYPE OF SAMPLE, FREQUENCY & AMOUNT: -

               N/A

9b   Would the sample be taken especially for this investigation rather than as part of normal   patient care?

9c   If taken especially for this investigation who will cover the costs of these tests?

10   Other tests to be administered:-
Questionnaires as described earlier

11a   Will any additional staff or facilities be required?

No
11b   If so, who will meet the cost of these requirements?

N/A

12   Procedures: describe the exact procedure which will be applied to each patient:-

All patients with implanted intrathecal drug administration systems and diagnosis of severe chronic non-malignant pain will be approached for recruitment consecutively. The study will be explained to them by Dr Raphael (Pain Consultant) and Ms Southall(Pain Nurse Practitioner) verbally and they will also be given written information. They will be given opportunity to think about it, discuss it and ask any questions. Those who give consent to enter the study will be randomised by random number into one of the two groups described earlier. They will be required to attend the pain unit weekly for 10 weeks for approximately half an hour to undergo computerised telemetric reprogramming of the pump and complete questionnaires.

At the end of the 10 week period, patients can opt to remain on their current dose or return to a previous dose. This choice will form part of data collection.

As described in the protocol , patients can withdraw from the study at any stage without prejuding their treatment.

13   Discomfort: what discomfort or interference with their activities may be suffered by all   or   any of the patients?

-5 -

Patients required to attend the clinic weekly for the 10 week study period (compared to routine of attendance every 6-12 weeks) for pump dose change and completion of questionnaires. Estimated total time each at visit is 30 minutes

14a   Hazards: are there any physical or mental hazards associated with these investigations?

Potentially less pain relief

14b   If so, what are these?

As above

14c   How do you assess the chances of such hazards occurring:-

                          Possible
15   In precisely what terms is it proposed to explain the project to potential subjects?

Patient information sheet(enclosed)

16a   Are any payments to be made for entering patients in this study? No
            If yes, how much?

16b   If so, to whom and how will the money be used. Please indicate as clearly as possible how the money generated from undertaking this trial will be utilised.

16c   It should be noted that any monies received by NHS clinicians for research carried out on patients in NHS facilities should be placed into accounts or Trust Funds which are available for financial audit.

            Will the monies you receive be placed into an account available for audit?

                          Yes
                          No

            If no what will happen to the monies received?

            Your attention is drawn to paragraph 120 of the GMC guidelines, Professional Conduct and Discipline: Fitness to Practise -

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"It may be improper for a doctor to accept per capita or other payments from a pharmaceutical firm in relation to a research project such as the clinical trial of a new drug, unless the payments have been specified in a protocol for the project which has been approved by the relevant national or local ethical committee. It may be improper for doctors to accept per capita or other payments under arrangements for recording clinical assessments of a licensed medicinal product, whereby they are asked to report reactions which they have observed in patients for whom they have prescribed the drug, unless the payments have been specified in a protocol for the project which has been approved by the relevant national or local ethical committee. It is improper for doctors to accept payment in money or kind which could influence their professional assessment of the therapeutic value of a new drug."

17   Have you enclosed a specimen of written consent form?

      Yes

18   Is it your intention to inform the patient's G.P of his/her inclusion in the study?

      Yes

19a   Will patient medical records be examined by research member(s) outside the   employment   of   the
NHS?

      Yes. Psychologist

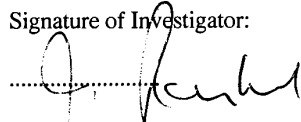19b   If yes above what steps will be taken to safeguard confidence?

      Clinician investigator will obtain honorary contract for patient contact.

The information supplied above is to the best of my knowledge and belief accurate. I understand my obligations and the rights of the patient, particularly the need to obtain freely given written informed consent.

Date of Submission: Signature of Investigator:

   4/4/02
....

To be completed by the Consultant in Charge or Head of Department

I have read through the study protocol and this form.
I hereby endorse this application with my approval:-

Signature: ....

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▬ CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	4.5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6,7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	8
	13b	For each group, losses and exclusions after randomization, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9,10
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

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Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain

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Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain

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Keywords: chronic pain; drug delivery systems, implantable; morphine; randomised controlled trial; treatment efficacy

Word count: 3,357

ABSTRACT

Objective

This study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity.

Design

Randomised, double blind, controlled, parallel group trial.

Setting

Department of Pain Management, Russells Hall Hospital, Dudley, United Kingdom.

Participants

Twenty-four non-cancer pain patients implanted with morphine reservoirs were assessed for eligibility.

Interventions

Participants were randomly allocated to one of two parallel groups in which one of the groups had no change in morphine dose and the other group had a small reduction (20%) in dosage every week during a 10-week follow-up.

Outcome

Primary outcomes were visual analogue scale (VAS) pain score change and withdrawal from study due to lack of efficacy.

Results

Nine of the patients assessed for eligibility declined to participate in the study. Fifteen patients were randomised to control (n=5) or intervention (n=10) and included in an intention-to-treat analysis. Due to worsening of pain, seven patients withdrew from the study prematurely. None knew prior to withdrawal which arm of the study they were in, but all turned out to be in the dose reduction arm. Calculation of drop-out rate between groups indicated a significant statistical difference (p=0.026) and recruitment was ceased. VAS change between baseline and last observation was smaller in the control group (Mdn=11) than in the intervention group (Mdn=30.5), although not statistically significant, Z=-1.839, p=0.070, r=-0.47. Within groups, VAS was significantly lower at baseline (Mdn=49.5) than at last observation (Mdn=77.5) for the reduction group, Z=-2.805, p=0.002, r=-0.627 but not for the control group (p=0.188).

Conclusion

This double blind RCT of chronic intrathecal morphine administration suggests effectiveness of this therapy for the management of chronic non-cancer pain. However, due to small number of patients completing the study (n=8) further studies are warranted.

2

Trial registration

International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

INTRODUCTION

Opioid receptors were identified in the spinal cord in 1973.[1] Subsequent animal studies demonstrated that intrathecal opioids produce powerful and highly selective analgesia.[2] Intrathecal opioids exert their analgesic effect pre and post synaptically by reducing neurotransmitter release and by hyperpolarising the membranes of neurones in the dorsal horn, thus inhibiting pain transmission.[3]

The technique of intrathecal drug delivery is based on the principle that effective analgesia can be achieved by the action of some drugs at the dorsal horn and adequate concentrations cannot be achieved by systemic administration, or only by high systemic doses. Delivery of the drug by the intrathecal route is a means of achieving these enhanced therapeutic effects. The smaller doses needed for intrathecal administration also allow a reduction in side effects compared to systemic administration. Following the first clinical use of epidural [4] and intrathecal opioids,[5] Cousins used the expression 'selective spinal analgesia' to describe the phenomenon that spinally administered opioids could produce a specific analgesic effect with few motor, sensory or autonomic side effects.[6] It was subsequently demonstrated that the analgesic effect was, in the main, due to the uptake of the opioid directly into the spinal cord and cerebrospinal fluid.[3]

Key indications for intrathecal drug delivery systems are chronic pain unresponsive to curative medical or surgical measures and to more conservative palliative measures including systemic analgesics, physical therapies, psychological therapies, perineural injection procedures and nerve lesioning procedure. Pathologies for the pain are broad and only exclude psychogenic pains; they can be due to cancerous or non-malignant pathologies. Morphine is considered the 'gold standard' medication for intrathecal drug delivery systems because of its stability, receptor affinity and extensive experience of using the drug by this route.[7]

For chronic non-malignant pain it is strongly recommended that patients have a comprehensive psychological assessment [8] to: (i) assess possible concurrent psychopathology (e.g. severe affective disorder, body dysmorphia, procedural fears) that might impede successful implantation; and (ii) consider what additional individualised preparation might be advisable for the patient.[9] Cognitive behavioural therapy should not be excluded as a subsequent treatment

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option. It may ensure that the reduction in pain severity expected as a result of the ITDD system is capitalized upon by the development of reduced pain related behaviours and increased activity in a range of adaptive behaviours.

The first reservoir for intrathecal analgesic delivery was implanted in 1981,[10] and since then continuous intrathecal analgesia using opioids and other analgesics has become a recognized therapy for the management of severe and otherwise intractable chronic pain despite a lack of well-controlled studies. A three-year prospective study of intrathecal opioid treatment for chronic non-cancer pain showed that when patients with extremely severe pain problems are selected for intrathecal drug delivery, they are likely to improve with the therapy but their overall severity of pain and symptoms still remains high.[11] At least minimally clinical important changes in pain intensity were observed in 95% of participants in a recent study with a mean follow-up duration of 13 years.[12] Improvements were also observed in sensory and psychosocial outcomes.

Recent systematic reviews were unable to find randomised controlled trials (RCTs) evaluating the effectiveness of long-term intrathecal drug delivery systems (IDDS) for the management of chronic non-cancer pain.[13,14] Overall, the use of intrathecal opioid administration seems beneficial but the current available literature is too sparse to draw definite conclusions mainly due to the quality of the evidence. A systematic review of multiple well-designed RCTs is considered the highest level of evidence for the efficacy of a pain treatment, followed by a well-designed RCT of adequate size as the next best level of evidence.[15] To our knowledge there is only one such study of intrathecal opioids and that is confined to cancer pain.[16]

In the absence of strong supporting evidence for the use of intrathecal opioids for chronic non-cancer pain, the therapy must be balanced against its risks as procedure related complications have been reported to occur at a rate of 0.29 events per patient year and catheter related complications at a rate of 0.05 events per patient year.[17] Possible infections include meningitis, epidural abscess, pump pocket infection or pump reservoir infection. The rate of meningitis reported by studies ranged from 2.3% to 15.4% and for wound infections from 4.2% to 8.8%.[18] When considering only non-cancer pain studies, the percentage of patients with meningitis ranged from 0% to 4% and for wound infections, from 0% to 22%.[19] Furthermore, less common but serious events of permanent neurological injury can occur due to development of opioid associated granulomata. The incidence for this adverse event has been reported as 0.04% after one year, increasing to 1.15% after six years.[20] The management of the different

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adverse events is varied as some acute side-effects may resolve with time (e.g. nausea, vomiting, dizziness, or itching). Recommendations for aftercare, on-going care, prevention and management of potential complications and side-effects has been described.[8,18]

We had previously undertaken a prospective controlled study, of single dose morphine compared with saline in patients with chronic non-malignant pain and demonstrated spinal morphine to be efficacious in the short term for patients who respond to systemic morphine but in whom side effects have become intolerable.[21] The current study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity. Our primary outcome was visual analogue pain score change and withdrawal from study due to lack of efficacy.

METHODS

Study design and participants

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462). We conducted a single centre, double-blind, equal randomization [1:1], dose reduction, controlled, parallel group study. All subjects provided written informed consent. The original protocol anticipated using diamorphine, but between trial approval and trial commencement, practice changed to using morphine and the protocol was amended to reflect this.

Treatment strategies for the management of chronic pain start with the lowest risk and least invasive intervention and progress if a treatment is not effective. IDDS is a last-resort treatment to treat severe chronic pain because of their invasive nature, concerns about long-term opioid use, and the possible complications related to the procedure. IDDS is considered for use in patients with chronic non-cancer pain after more conventional treatments have failed (e.g. pharmacotherapy, transcutaneous electrical stimulation or in some cases spinal cord stimulation) and in those who respond to systemic opioids but the side effects have become intolerable. Patient suitability is also determined by a multidisciplinary team assessment that includes a clinical psychologist. A biopsychosocial history is performed, in which factors such as organic cause of pain, topography, duration of pain, pain intensity, coping strategies, social support, medico legal matters, history of anxiety and/or depression, previous treatments, and

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drug and/or alcohol abuse is taken into consideration. Where there is discrepancy across the clinical team of physician, physiotherapist, psychologist and specialist nurse, a case conference is set up to include the family physician, and other psychologists, physiotherapists and physicians not directly involved in intrathecal therapy.

Following multidisciplinary assessment all patients have an inpatient trial of intrathecal therapy prior to implantation. This is conducted by repeated bolus of morphine and saline in a single blind fashion.[21] Patients reporting greater than 50% relief with morphine and less with saline are selected for IDDS. Chronic dosing is extrapolated and titrated at refills (approximately two per month initially). A small increase in opioid dose may be necessary to maintain an adequate pain control. Recent observations indicate that significant differences cease following year 3 of therapy suggesting stability.[12] Additional intrathecal drugs were added if level of analgesia is inadequate as per polyanalgesic consensus conference algorithm.[22] Adjuvant intrathecal medication such as bupivacaine may contribute to achieve better pain control and to maintain low intrathecal morphine doses in cancer [23] and non-cancer patients.[24]

Eligible participants were adults aged 18 or over with implanted intrathecal reservoirs of programmable type (Synchromed, Medtronic Ltd) receiving intrathecal morphine for non-cancer pain and having had infusion for ≥ 12 months. Patients had reported a stable level of analgesia with the pump, based upon their attendance for pump refills at which dose did not change and they reported analgesia. In view of the need for weekly attendance during the study only those patients living within a short time journey from the hospital, with access to transport and limited co-morbidities were considered.

The pain nurse approached eligible patients for consent and patients were randomly assigned by computer generated randomization (PN) to one of two parallel groups in which one of the groups had no change in the morphine dose (control group) and the other group had a small reduction (20%) in the preceding week dose every week during participation in the study (intervention group). The allocation sequence was received in sequentially numbered, opaque and sealed envelopes to ensure that the sequence was concealed. Patients were unaware as to which group they were in, as the dose alteration or no change was conducted by telemetry with the screen not visible to the patient. The telemetry was conducted by a physician (JHR) who was the only investigator aware of the allocation. Pain scores and other outcome measures were collected by a researcher (RVD) blinded to the allocation of the patients.

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Outcome measures

Primary outcome measures were visual analogue scale (VAS) [25] score for pain and withdrawal from study. Secondary outcome measures were functional and psychological measures based on Oswestry Disability Index (ODI),[26] Hospital Anxiety and Depression scale (HAD)[27] and Coping Strategies Questionnaire (CSQ).[28] Subjects were evaluated at baseline and each week during participation in the study. VAS and ODI were collected on a weekly basis. HAD and CSQ were collected fortnightly.

Patients were asked to rate their average pain intensity during the previous week using a VAS. The VAS consists of a 100 mm straight line with anchors at its ends labelled as no pain and worst pain imaginable. The VAS is a recognised method for the assessment in variation of pain intensity.[25,29] Clinically important changes were classified in accordance with a consensus statement that established a 10-20% decrease as minimally important, ≥ 30% as moderately important and ≥ 50% as a substantial change.[30]

The ODI is used to assess the level of pain interference with various activities of daily living. The ODI is a valid measure of condition-specific disability.[31] The ODI consists of 10 items/activities with 6 levels (range 0-5). Scoring of this questionnaire was calculated as recommended by Fairbank and Pynsent.[31]

The HAD scale is a self-report rating scale of 14 items with 4 levels (range 0-3). This scale is used to screen for anxiety and depression (7 intermingled items for each subscale). The total score for each subscale is the sum of the respective seven items (ranging from 0–21). The HAD scale is considered a valid instrument for detecting states of anxiety and depression.[32]

The CSQ is a self-report instrument to assess active and passive coping skills of chronic pain patients.[33] The CSQ includes cognitive coping strategies (diverting attention, reinterpreting pain sensation, catastrophising, ignoring pain sensations, praying or hoping, coping self-statements), behavioural coping strategies (increasing activity level), and effectiveness ratings (control over pain, ability to decrease pain). Scores of these subscales result in 3 factors that account for 68% of the variance in questionnaire responses (cognitive coping and suppression, helplessness, diverting attention and praying). This questionnaire is a valid and reliable tool for chronic pain patient assessment.[28]

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Data analysis

An *a priori* power analysis based on previous open study data of reduction in VAS for pain with intrathecal therapy [21] computed a sample size of 24 (12 per group) would provide 80% power at the 5% significance level to detect a difference in the means of 1.2 standard deviations (unpaired t test) or a difference between the two proportions 20% and 80% (Fisher's Exact Test). The power analysis was based on a study which compared one group receiving morphine with one group receiving placebo (saline). The difference in means in the pilot study (5.1-0.91 = 4.19) was not used as the basis for the power calculation as the difference in the pilot study was likely to be larger than the difference observed in the current study where both groups received morphine. A difference in the means of 1.2 standard deviations was considered as a realistic estimate since we allowed for the effect to be much smaller than that observed in the pilot study (2.6 standard deviations if the standard deviations of 1.3 and 1.9 are pooled). Imputation methods were not used since the drop-out rate in the group randomised to have intrathecal dose reduction was 70%. This high drop-out percentage rate would bias the results regardless of the imputation technique employed. Therefore, we followed an intention-to-treat protocol; all subjects were included in the analysis and this was limited to within and between-group comparisons of baseline and final observation scores.

Kolmogorov-Smirnov test was performed to test normality of numerical data. The majority of the numerical data was not normally distributed and attempts to transform the data were unsuccessful. Therefore, differences between patient baseline characteristics were performed using the Mann-Whitney U test. Differences between baseline and last observation scores were evaluated using Wilcoxon Signed Ranks test. Categorical variables were investigated using Fisher's exact test. Data is reported as median (minimum-maximum). Statistical significance was judged at 5% level. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0, SPSS Inc., Chicago, IL, USA).

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RESULTS

Between 2006 and 2011, 24 patients were assessed for eligibility, nine declined to participate. Following inclusion in the study of 15 patients, it was observed that a high rate of patients withdrew from the research (Figure 1). Because of the large number of withdrawals, a first interim analysis was undertaken just beyond half way point which revealed that the withdrawals were all from the group randomised to have dose reduction. The drop-out rate in the group randomised to have intrathecal dose reduction was 70% and there were no drop-outs in the patients allocated to the control (no dose reduction) group. One subject left the study following week 1, three patients withdrew after week 2, two participants after week 5 and one patient after week 7. The intrathecal opioid dose in the patients that withdrew from the study was reduced from a median of 1.6 mg/day (0.625 – 5.5) to 1.15 mg/day (0.4 – 2.8) which corresponds to a decrease of 36% (20 - 79) in the intrathecal opioid dose. The reason for drop-out from the study was related with worsening of pain for all the participants. Calculation of drop-out rate between the groups indicated a significant statistical difference (p = 0.026). Recruitment ceased at that moment.

(Insert Figure 1/flow diagram here)

The patients recruited comprised 8 men (53.3%) and 7 women (46.7%) with a median age at the moment of enrolment in the study of 58 years (45-68). The median duration of IDDS therapy prior to participation in this study was 26 months (12-180). The pain syndrome was mechanical nociceptive caused by degenerative low back pain in 5 (33.3%) of the participants; visceral nociceptive due to post surgery abdominal pain in 1 (6.7%) patient and mixed nociceptive-neuropathic following failed back surgery syndrome in 9 (60%) subjects. The 5 patients in the control group comprised 2 with mechanical back pain and 3 with failed back surgery syndrome; the 10 in the intervention group comprised 3 with mechanical back pain, 6 with failed back surgery syndrome and 1 with post-surgery abdominal pain. All patients had been on systemic opioids prior to pump implantation and thereafter only took opioids intrathecally. The preparations differed and the equivalent oral morphine dose prior to implant ranged from 20 to 240mg morphine equivalent per day (Table 1 and 2).

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Table 1. Baseline characteristics of the patients according to randomization group

Characteristic	Control group (n = 5)	Intervention group (n = 10)	Test statistic	P
Age (years)	55 (45 - 59)	64 (52 - 68)	$Z = -1.719$	0.095
Gender (M/F)	4/1	4/6		0.282
Duration of therapy (months)	66 (22 - 88)	20.5 (12 - 180)	$Z = -1.191$	0.265
Pre-implant oral morphine dose mg/day	60 (20 - 120)	50 (40 - 240)	$Z = -0.638$	0.579
Morphine dose mg/day	4.625 (2.125 - 5.65)	1.612 (0.625 – 5.5)	$Z = -2.205$	0.028
Adjuvant intrathecal medication (Y/N)	4/1	5/5		0.580
Bupivacaine dose mg/day	3.190 (2.05 - 4.433)	2.050 (1.65 - 2.122)	$Z = -1.715$	0.111
Visual Analogue Scale	59 (0 - 69)	49.5 (10 - 64)	$Z = -1.043$	0.323
Oswestry Disability Questionnaire	54 (12 - 64)	55.85 (42 - 72)	$Z = -0.677$	0.529
Hospital Anxiety and Depression scale				
HAD anxiety	8 (2 - 16)	7.5 (1 - 12)	$Z = -0.369$	0.745
HAD depression	7 (2 - 11)	7.5 (2 - 15)	$Z = -0.802$	0.450
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	11.5 (0 - 31)	$Z = -0.147$	0.918
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	$Z = -0.477$	0.690
Catastrophising	7 (2 - 31)	22 (1 - 27)	$Z = -0.147$	0.911
Ignoring pain sensations	8 (3 - 21)	8 (0 - 28)	$Z = -0.221$	0.862
Praying or hoping	14 (2 - 26)	18.5 (0 - 30)	$Z = -0.366$	0.753
Coping self-statements	25 (15 - 30)	19 (2 - 32)	$Z = -0.954$	0.375
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	$Z = -0.366$	0.753
Control over pain	2 (1 - 5)	3 (1 - 4)	$Z = -0.301$	0.757
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	$Z = -0.846$	0.543
Cognitive coping and suppression	32 (18 - 70)	32.5 (6 - 83)	$Z = -0.293$	0.833
Helplessness	-7 (-14 - 10)	2 (-36 - 11)	$Z = -0.806$	0.458
Diverting attention and praying/hoping	26 (2 - 54)	31.5 (0 - 56)	$Z = -0.440$	0.698

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented p < 0.05

There were no statistically significant differences between the groups at baseline for age, gender, duration of therapy prior to study, adjuvant intrathecal medications, VAS, ODI, HAD scale and CSQ (Table 1). The intrathecal opioid dose administered at study entry was significantly higher in the control group (*Mdn* = 4.625) than in the intervention group (*Mdn* = 1.612), a chance finding, $U = 7.00$, $p = 0.028$, $r = -0.57$. A comparison of baseline scores between patients who completed the study and those that did not complete demonstrates non-

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significant differences for all the variables, including intrathecal dose administered at start of investigation (Table 2).

Table 2. Baseline characteristics of the patients according to completion of study

Characteristic	Complete (n = 8)	Incomplete (n = 7)	Test statistic	P
Age (years)	56.5 (45 - 68)	64 (53 - 66)	Z = -1.102	0.296
Gender (M/F)	6/2	2/5		0.132
Duration of therapy (months)	25 (15 - 88)	27 (12 - 180)	Z = -0.081	0.960
Pre-implant oral morphine dose mg/day	60 (20 - 120)	60 (40 - 240)	Z = -0.241	0.869
Morphine dose mg/day	3.065 (1.02 - 5.65)	1.6 (0.62 – 5.5)	Z = -1.273	0.232
Adjuvant intrathecal medication (Y/N)	5/3	4/3		1.000
Bupivacaine dose mg/day	2.5 (1.7 – 4.25)	2.085 (1.86-2.12)	Z = -0.735	0.556
Visual Analogue Scale	44.5 (0 - 69)	54 (23 - 64)	Z = -0.522	0.632
Oswestry Disability Index	53 (12 - 64)	57.7 (42 - 72)	Z = -1.222	0.244
Hospital Anxiety and Depression scale				
HAD anxiety	7 (2 - 16)	8 (1 - 12)	Z = -0.116	0.934
HAD depression	9 (2 - 15)	7 (2 - 12)	Z = -0.816	0.447
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	13 (0 - 31)	Z = -0.501	0.649
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.466	0.714
Catastrophising	22 (2 - 31)	15 (1 - 27)	Z = -0.575	0.608
Ignoring pain sensations	8 (0 - 21)	8 (0 - 28)	Z = -0.215	0.861
Praying or hoping	15 (2 - 30)	18.5 (0 - 25)	Z = -0.358	0.760
Coping self-statements	24 (13 - 30)	19 (2 - 32)	Z = -0.358	0.755
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.143	0.916
Control over pain	2 (1 - 5)	3.5 (2 - 4)	Z = -1.101	0.317
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -1.050	0.386
Cognitive coping and suppression	32 (12 - 70)	32.5 (6 - 83)	Z = -0.000	1.000
Helplessness	-5 (-14 - 11)	0 (-36 - 10)	Z = -0.215	0.868
Diverting attention and praying/hoping	27 (2 - 54)	31.5 (0 - 56)	Z = -0.287	0.809

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented $p < 0.05$

The VAS change between baseline and last observation was lower in the control group (Mdn = 11) than in the intervention group (Mdn = 30.5), although not statistically significant, $Z = -1.839$, $p = 0.070$, $r = -0.47$ (Table 3). There were no statistically significant differences between the randomised groups in the changes detected for ODI, HAD scale anxiety and depression and all items of CSQ between baseline score and final observation.

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Table 3. Changes between baseline and last observation

	Control group (n = 5)	Intervention group (n = 10)	Test statistic	P
VAS	11 (-4 - 40)	30.5 (2 - 77)	Z = -1.839	0.070
ODI	12 (4 - 18)	6 (-2 - 30)	Z = -1.070	0.311
HAD anxiety	1 (-6 - 3)	0.5 (-3 - 5)	Z = -0.523	0.653
HAD depression	0 (-1 - 3)	0 (-3 - 6)	Z = -0.074	0.959

Median (minimum-maximum); variables analysed using Mann-Whitney U test (Exact sig. (2-tailed))

Within group comparisons were also carried out (Table 4). Statistically significant differences for VAS were observed between baseline and last observation in the group randomised to have dose reduction (intervention) but not in the control group (*p* = 0.188). The VAS was significantly lower at baseline (*Mdn* = 49.5) than at last observation (*Mdn* = 77.5) for the intervention group, *Z* = -2.805, *p* = 0.002, *r* = -0.627 (Figure 2). The ODI scores at baseline (*Mdn* = 55.85) were significantly lower than at last observation (*Mdn* = 68.40) for the group allocated to have dose reduction, *Z* = -2.201, *p* = 0.027, *r* = 0.492. No statistically significant differences were observed for the ODI in the control group (*p* = 0.063). There were no statistically significant changes detected for HAD scale anxiety and depression and all items of CSQ in either randomised group between baseline score and final observation.

Table 4. Within group analysis for VAS and ODI

		VAS	ODI
Control group (n = 5)	Baseline	59 (0 - 69)	54 (12 - 64)
	Last observation	70 (40 - 83)	64 (30 - 74)
	Test statistic	Z = -1.625	Z = -2.032
	P	0.188	0.063
Intervention group (n = 10)	Baseline	49.5 (10 - 64)	55.85 (42 - 72)
	Last observation	77.5 (57 - 100)	68 (48 - 84)
	Test statistic	Z = -2.805	Z = -2.201
	P	0.002	0.027

Median (minimum-maximum); variables analysed using Wilcoxon test (Exact sig. (2-tailed))

The calculation of clinical changes based on the VAS scores indicated non-significant clinical changes in 10% of the patients in the dose reduction group (intervention), minimally clinically important changes (≥10% and <30%) were observed in 20% of the participants randomised to this group, moderately important increase in pain (≥30% and <50%) in 40% of the subjects and substantially important increase in pain (≥50%) in 30% of the patients. For the group where the

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morphine dose remained the same (control), non-significant changes were observed in 40% of the sample, minimally clinically important changes (≥10% and <30%) in 40% of the participants and one patient (20%) had a clinically substantial increase in pain.

(Insert Figure 2 here)

DISCUSSION

This randomised controlled trial of intrathecal opioid therapy in chronic non-malignant pain has demonstrated differences in pain relief between dose reduction and dose maintenance. It lends support to the efficacy of this therapy, which until now has not been subject to controlled trials.

A power analysis indicated that 24 patients would need to be included in the study to obtain a power of 0.8; however, due to high number of withdrawals, we undertook an interim analysis in which we found that the withdrawals were all in the dose reduction arm. The attrition rate of 70% in the group randomised to have reduction also indicates that the treatment seems to be effective. Statistically significant differences between the arms were observed and the study was stopped. Although not statistically significant, the VAS change between baseline and last observation was lower in the control group than in the reduction group. Within group VAS and ODI differences were statistically significant between baseline and last observation for the treatment arms with statistically significant greater pain and worsened disability in the dose reduction arm. Clinically important changes indicating an increase in pain intensity were observed in 90% of the patients randomised to dose reduction (intervention). These changes were moderately important (≥30% and <50%) in 40% of the patients and substantially important (≥50%) in 30% of the participants.

Significant differences between groups at enrolment were observed for morphine dose. The dose maintenance group (control) were found to have a significantly higher starting opioid dose. This mirrored the statistically insignificant trend towards longer duration of intrathecal therapy. It is possible that this group had greater levels of pain than the intervention group for the same dose of opioid and/or that with longer duration of therapy, the dose had increased with time, as a small increase in opioid dose may be necessary to maintain an adequate pain control and recent observations from our unit indicate that significant differences cease following year 3 of therapy suggesting stability.[12] When dose escalation occurs, it is usually due to tolerance, progress of the disease [34] or opioid induced hyperalgesia.[35]

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All subjects had stable levels of opioid delivery as evidenced by no change in delivered dose at recent refills before investigation and all reported analgesia with comparable pain scores (VAS). In using percentage dose reduction in this study, we anticipated overcoming a potential bias from this. Furthermore, no significant differences were observed at enrollment between those who completed the study and those who withdrew before completion, indicating that the initial opioid dose did not impact on drop-out rate. We had purposely chosen a small decrease of dose (20%) to avoid the patients suffering any withdrawal symptoms and none occurred. This parallels the experience of Rauck and colleagues in a study of opiate reduction within the context of investigating ziconotide.[36] In this study there was a 3 week weaning period prior to entering the trial and thus the weekly reduction in IT opioids would therefore be approximate to 30%. The weaning process was successful in 92.9% of the patients, only 14 dropped out due to inability to tolerate withdrawal, adverse events, noncompliance or patients request.

This study has recognised weaknesses of small sample size and being conducted in a single centre. The sample size was inferior to the 24 patients indicated by the a priori power analysis as the study was stopped when an interim analysis was conducted due to large number of drop-outs and revealed significant differences for withdrawals between groups. There was an imbalance in the number of patients in each group. The patients were randomised as a single block of 24, thus ensuring that in a sample of 24 there would be 12 in each group. Randomisation of smaller blocks would ensure that there were equal numbers in each group for smaller sample sizes as well (e.g. if we had used a block size of 6, we would have had equal numbers in each group after 6, 12, 18 and 24 patients had been randomised). With our single block of 24, the chance of getting a split as uneven as 10 and 5 after 15 patients was about 9%. This RCT was conducted in a single centre. Selection for therapy followed the national guidelines;[8] however, their interpretation may vary in clinical practice even within the same country in the psychosocial domains of pain. Dose titration strategies may differ across treatment centres. Different centres have reported average doses of 4.7 mg/day at an average of 3.4 years,[37] 7.42 mg/day at 29.14 months,[38] 9.6 mg/day at year 1 [39] and 12.2 mg/day at year 3.[40] This may lead to different levels of opioid delivery for which the sensitivity to dose reduction may differ.

The strengths of this study were not looking in the period following intrathecal drug delivery implantation because we considered that this period is confounded by need for dose titration

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and the non-specific psychological effects of a major intervention. In investigating patients with intrathecal delivery for a minimum of 12 months, we have been able to focus on evaluation of long term efficacy of intrathecal opioid therapy. To our knowledge this is the first randomised double-blind controlled study of this therapy in non-cancer pain. The findings of our randomised controlled trial suggest the efficacy of intrathecal morphine for the management of chronic non-cancer pain. Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction. In the light of these results, investigation of different populations and larger cohorts are recommended.

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Figure legends

Figure 1. Flow chart of patient participation

Figure 2. Individual visual analogue scale scores at baseline and final observation for control group (n=5) and reduction group (n=10).

ARTICLE SUMMARY

Article focus

- Recent systematic reviews were unable to find randomised controlled trials evaluating the effectiveness of long-term intrathecal drug delivery systems for the management of chronic non-cancer pain.

- We aimed to investigate if a small decrease in the intrathecal morphine dose leads to an increase in reported pain scores in chronic non-cancer pain patients undertaking long-term intrathecal morphine.

- The randomised controlled trial design would allow to investigate the long-term efficacy of intrathecal morphine delivery.

Key messages

- Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction.

- The findings of this study suggest the efficacy of intrathecal morphine delivery for the management of chronic non-cancer pain.

Strengths and limitations of this study

- To our knowledge, this is the first randomised controlled trial investigating the efficacy of intrathecal drug delivery systems for the management of chronic non-cancer pain.

- By investigating patients with intrathecal delivery for a minimum of 12 months this study is not confounded by need for dose titration and the non-specific psychological effects of a major intervention.

- Limitations of this study include small sample size and being conducted in a single centre.

Acknowledgments

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Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

JHR designed and was responsible for the conception of the trial. JHR, RVD, JLS, PN, GDK have made substantial contributions to (1) the acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

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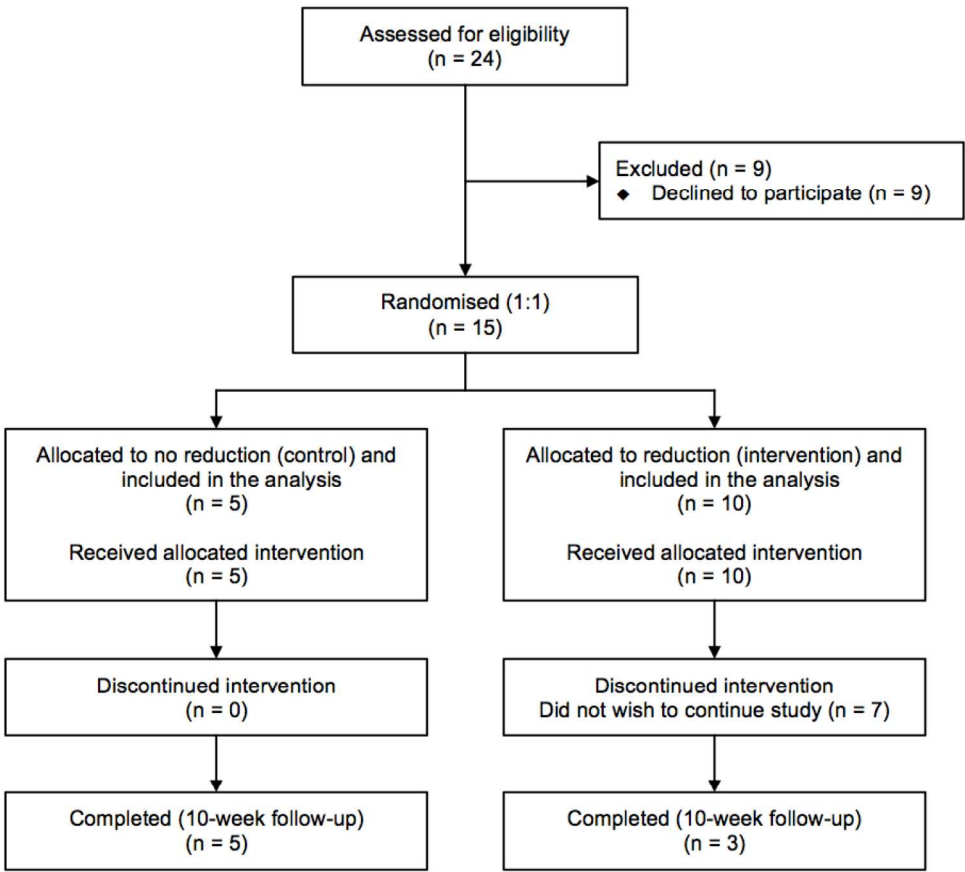
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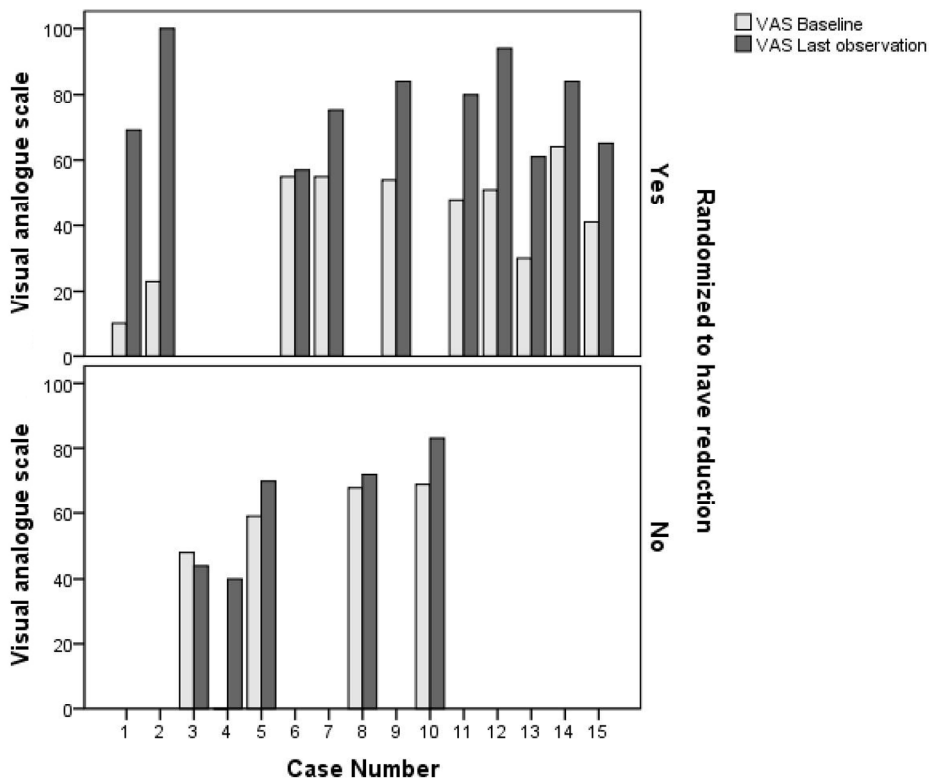Figure 1. Flow chart of patient participation
331x295mm (300 x 300 DPI)

Figure 2. Individual visual analogue scale scores at baseline and final observation for control group (n=5) and reduction group (n=10)
441x353mm (300 x 300 DPI)

Birmingham and The Black Country **NHS**
Health Authority

Dudley Local Research Ethics Committee
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REC/38/02/JUN   Please quote this number on all correspondence

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23 July 2002

Dr J Raphael
Consultant in Pain Management
Russells Hall Hospital
DUDLEY
West Midlands
DY1 2HQ

Dear Dr Raphael

Research Protocol: REC/38/02/JUN; Randomised controlled trial of intrathecal diamorphine in the treatment of chronic non-malignant pain

The Dudley REC reviewed your application on Friday 21 June 2002. The documents reviewed were as follows:

- **Application Form (No Version Dated: 04/04/02)**
- **Patient information sheet and consent form (No Version No Date)**
- **Questionnaire (No Version No Date)**

The members of the Committee present agreed there is no objection on ethical grounds to the proposed study. I am, therefore, happy to give you the favourable opinion of the committee on the understanding that you will follow the conditions set out below:

Conditions

- You do not recruit any research subjects within a research site unless favourable opinion has been obtained from the relevant REC.

- You do not undertake this research in an NHS organisation until the relevant NHS management approval has been gained as set out in the Framework for Research Governance in Health and Social Care.

Minicom: (Text Phone Users) 01384 243187
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REC/35/02/JUN

- You do not deviate from, or make changes to, the protocol without prior written approval of the REC, except where this is necessary to eliminate immediate hazards to research participants or when the change involves only logistical or administrative aspects of the research. In such cases the REC should be informed within seven days of the implementation of the change.

- You complete and return the standard progress report form to the REC one-year from the date on this letter and thereafter on an annual basis. This form should also be used to notify the REC when your research is completed and in this case should be sent to this REC within three months of completion.

- If you decided to terminate this research prematurely you send a report to this REC within 15 days, indicating the reason for the early termination.

- You advise the REC of any unusual or unexpected results that raise questions about the safety of the research.

- Note that the LREC approval is necessary but not sufficient for you to undertake this research project within your local NHS organisation and you will require separate approval from your organisation's Research and Development Directorate/ management in accordance with the research governance framework. Care should also be taken to ensure with the NHS organisation that local indemnity arrangements are adequate.

Any comments the REC wished to make are contained in the attached REC Response Form. The project must be started within three years of the date on this letter.

Yours sincerely

Dr Chris Spencer-Jones
CHAIR

cc   Mrs M Marriott, R & D Department

<div style="text-align:center">

RESEARCH ETHICS COMMITTEE
RESPONSE FORM

</div>

DETAILS OF APPLICANT:

1.   **Name and address of Principal Researcher:** Dr Jon Raphael, Consultant in
      Pain Management, Russells Hall Hospital, Dudley, West Midlands

2.   **Title of project:** Randomised controlled trial of intrathecal diamorphine in the
      treatment of chronic non-malignant pain

3.   **Name and address of Sponsor:**

DETAILS OF REC:

4.   **Name and address of REC:** Dudley REC, 12 Bull St, DUDLEY, West Midlands

5.   **REC Reference Number:** REC/38/02/JUN

**Listed below is a complete record of the review undertaken by REC with the decisions
made, dates of decisions and the requirements at each stage of the review:**

21/06/02

- *It was agreed that the design of this research application was sound and should
  provide useful information. There was a question of the practicalities of using
  diamorphine which is unstable and can be made up locally vs morphine that is
  stable and can be prepared in sterile conditions. The committee asked Dr Raphael
  to look into past infection rates using pumps and if there is a case for using sterile
  preparations. Any risk should be discussed with the Trust's Clinical Governance
  Department. Should there be a case for using morphine Dr Raphael should liaise
  with Ron Pate*

THE FINAL DOCUMENTS AND ARRANGEMENTS APPROVED BY THE REC

The following items have been approved by the Dudley REC:

Protocol [No Version Dated: 04/04/02]
Subject information sheet [No Version No Date]
Subject consent form [No Version No Date]
Subject questionnaire [No Version No Date]

Date of approval: **June 21 2002**

Signature of Chair/Administrator: Date:

Name *(please print)*:   DR CHRIS SPENCER JONES

DUDLEY PAIN MANAGEMENT SERVICE

Jon Raphael MD MSc (Pain)
Consultant in Pain Medicine

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JR/JH

27 January 2005

Dr J Neilson
Chairman
Research Ethics Committee
Haematology Department
Russells Hall Hospital

Dear Jeff

REC/38/02/JUN. RANDOMISED CONTROLLED TRIAL OF
INTRATHECAL DIAMORPHINE IN THE TREATMENT OF CHRONIC
NON MALIGNANT PAIN

In the middle of 2004 there was a directive from the Medical Devices Agency that recommended Diamorphine no longer be used in intrathecal programmable pumps because of a few reports of mechanical pump failure. It was thought that this was related to the mono acetate metabolite of Diamorphine. Accordingly we are following the recommendations of the Pain Society and all new implanted pumps are now filled with Morphine and we are in the process of converting the existing pumps from Diamorphine to Morphine. As you will appreciate since April 2004 we have not recruited anybody to this study. We would, however, like to continue with this research in respect of intrathecal Morphine as opposed to Diamorphine. Since Diamorphine very rapidly breaks down to Morphine and when administered intrathecally they are equivalent in dose (as shown in publication with Mourad Labib) we would like to continue with the same protocol except but substituting the word Diamorphine for Morphine throughout. The design of the study is a percentage dose reduction protocol, the reported efficacy and side effects of intrathecal Morphine are same as Diamorphine and therefore, we do not require to change the protocol in other respect. I look forward to hearing from you.

With kind regards,
Yours sincerely

dictated but not signed

Jon Raphael MD MSc (Pain)
Consultant in Pain Medicine

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DESCRIPTION OF RESEARCH PROJECT FOR SUBMISSION TO THE DUDLEY LOCAL RESEARCH ETHICS COMMITTEE

NOTE: ALL QUESTIONS MUST BE ANSWERED BY THE PERSON ACTUALLY UNDERTAKING THE RESEARCH.
ANSWERS MUST BE TYPEWRITTEN. ANY FORMS NOT COMPLETED IN TYPE WILL BE RETURNED

1   Name(s) of Responsible Investigator(s):-

Jointly_
Jon Raphael, Consultant in Pain Management, Dudley GOH
David Booth, Professor of Psychology, Univ of Birmingham
George Kitas, Consultant Rheumatologist, Dudley GOH

2   Please advise the number of other trials/studies in which the local investigator
          a) is currently involved?
               5

          b) has been involved in the last six months?
               as above

2a   Title of Project:-

Randomised controlled trial of intrathecal diamorphine in the treatment of chronic non-malignant pain

2b   Clinical Trial Certificate Reference or Exemption Certificate Reference:-

         N/A

3a   Objective (i.e. hypothesis which it is intended to test):-

1. Intrathecal opioids are useful in the treatment of severe chronic non-malignant pain

2. Therapeutic efficacy is dose-dependent

3. Gradual reduction of intrathecal opioid dose is safe

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3b What practical benefit do you envisage from a successful completion of this project?

Production of evidence of good scientific quality that this therapeutic approach is useful (or not) in severe chronic non-malignant pain

Identification of the most appropriate diamorphine dose that should be used for treatment, with the minimum potential for side effects

4 Design of the Study (describe briefly):-

Patients will be recruited from those already with an implanted intrathecal drug delivery system providing diamorphine for chronic non-malignant pain.

All patients meeting above criteria will be approached for recruitment and those who consent to enter this study will be randomised by random numbers generator into one of two groups:

Group 1 will have the dose of diamorphine reduced every week by 20% of the preceeding weeks dose for 10 weeks.

week	dose (as percentage of starting dose)
0	100%
1	80
2	64
3	51
4	41
5	33
6	25.5
7	20.5
8	16.5
9	13
10	10

Group 2 has no change in dose at these weekly visits.
The above changes are made by computer telemetry to which patient is blinded.

Measurements will be made at these weekly visits as follows:
1. Pain will be measured using Visual Analogue Scale (VAS)
2. Function will be measured by the Ostwestry Disability Score (ODS)
3. Psychological parameters will be measured by the Hospital Anxiety Depression Score (HAD) and the Pain Coping Strategies Questionnaire (PCSQ)
4. Sociological parameters will be measured by the Short Form-36 Questionnaire (SF-36)
5. An overall assessment of change will be measured by the Global Impression of Change (GIC).

Endpoint will be withdrawal due to inefficacy or withdrawal due to side effects

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5a   Scientific background: give a brief account:-

Chronic non-malignant pain has enormous social and economic consequences (CSAG, 1994). A wide variety of treatments are used including drugs, physical therapies, operations and psychological treatments. Although they appear to help some patients and many have been subjected to studies that support their benefit, there remain a number of patients who continue despite this to have severe chronic and disabling pain.

The discovery of opioid receptors in the spinal cord led to the rationale use of intrathecal opioids for pain relief (Wang, 1979). This was initially used in those patients with cancer. With the development of implantable, programmable, continuous drug delivery systems in the 1980s, the use of intraspinal opioids was extended to non-cancer pain.

Published data on the outcome of this therapy is limited to retrospective studies from the USA (Paice, 1996), Europe (Winkelmuller, 1996) and the UK (Raphael, 2000). Nevertheless , these studies consistently support its benefits in alleviating pain and improving quality of life as reported by the National Institute of Clinical Excellence (NICE) (Williams, 2001). It also appears to be cost effective since less drugs and other treatments are needed after spinal pump implantation (Mueller-Schwefe, 1999).

The NICE document expressed the need for comparator studies to provide more robust data and I am in the process of designing a multi-centre prospective randomised placebo controlled trial to address this in new patients in liason with the Birmingham Clinical Trials Unit. However, a lot can be learnt from patients already receiving this therapy. These cannot be randomised in a placebo controlled trial because opioid withdrawal would lead to unacceptable side effects. They can be randomised to a dose-ranging trial as described above which will produce information about the efficacy (or not) of this therapy and the optimum dose.

5b   Has the investigation been done previously with human subject?

No

5c   If so, why repeat it?

6a   Subjects:How many are needed?

Power calculations have been based on previous open study with pain as primary outcome. 24 patients are required in total (12 per group) to provide 80% power at the 5% significance level

             and how selected?

-3 -

Patients receiving intrathecal diamorphine for chronic non-malignant pain by implanted computerised drug delivery system. As the regional centre for this therapy we have sufficient patients attending for follow up to acheive the required sample size.

6b Are the patients included in this study involved in any other research investigation at the present time?

No

6c Controls: how many are needed?

12 (described above)

6d What is the primary end point?
Pain relief by VAS
Withdrawal from protocol due to inefficacy

7a Have you taken any statistical advice on the numbers required for your study to give scientific
validity

    YES

7b If YES from whom was the advice obtained?

D. Booth, Professor of Health Psychology, Univ of Birmingham

7c If NO why not?

N/A

8a Substances to be given to the subjects (special diets, drugs, isotope tracers etc):-

STATE ROUTE OF ADMINISTRATION, AMOUNT & EFFECTS ANTICIPATED:

N/A

8b Who will cover the costs of these substances?

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8c   How will they be stored and issued?

9a   Samples to be taken from the subjects (venepuncture, arterial, urine, biopsy etc):

          STATE TYPE OF SAMPLE, FREQUENCY & AMOUNT: -

                    N/A

9b   Would the sample be taken especially for this investigation rather than as part of normal   patient care?

9c   If taken especially for this investigation who will cover the costs of these tests?

10   Other tests to be administered:-
Questionnaires as described earlier

11a   Will any additional staff or facilities be required?

No
11b   If so, who will meet the cost of these requirements?

N/A

12   Procedures: describe the exact procedure which will be applied to each patient:-

All patients with implanted intrathecal drug administration systems and diagnosis of severe chronic non-malignant pain will be approached for recruitment consecutively. The study will be explained to them by Dr Raphael (Pain Consultant) and Ms Southall(Pain Nurse Practitioner) verbally and they will also be given written information. They will be given opportunity to think about it, discuss it and ask any questions. Those who give consent to enter the study will be randomised by random number into one of the two groups described earlier. They will be required to attend the pain unit weekly for 10 weeks for approximately half an hour to undergo computerised telemetric reprogramming of the pump and complete questionnaires.

At the end of the 10 week period, patients can opt to remain on their current dose or return to a previous dose. This choice will form part of data collection.

As described in the protocol , patients can withdraw from the study at any stage without prejuding their treatment.

13   Discomfort: what discomfort or interference with their activities may be suffered by all   or   any
of the patients?

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Patients required to attend the clinic weekly for the 10 week study period (compared to routine of attendance every 6-12 weeks) for pump dose change and completion of questionnaires. Estimated total time each at visit is 30 minutes

14a   Hazards: are there any physical or mental hazards associated with these investigations?

Potentially less pain relief

14b   If so, what are these?

As above

14c   How do you assess the chances of such hazards occurring:-

Possible

15   In precisely what terms is it proposed to explain the project to potential subjects?

Patient information sheet(enclosed)

16a   Are any payments to be made for entering patients in this study? No
If yes, how much?

16b   If so, to whom and how will the money be used. Please indicate as clearly as possible how the money generated from undertaking this trial will be utilised.

16c   It should be noted that any monies received by NHS clinicians for research carried out on patients in NHS facilities should be placed into accounts or Trust Funds which are available for financial audit.

Will the monies you receive be placed into an account available for audit?

Yes
No

If no what will happen to the monies received?

Your attention is drawn to paragraph 120 of the GMC guidelines, Professional Conduct and Discipline: Fitness to Practise -

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"It may be improper for a doctor to accept per capita or other payments from a pharmaceutical firm in relation to a research project such as the clinical trial of a new drug, unless the payments have been specified in a protocol for the project which has been approved by the relevant national or local ethical committee. It may be improper for doctors to accept per capita or other payments under arrangements for recording clinical assessments of a licensed medicinal product, whereby they are asked to report reactions which they have observed in patients for whom they have prescribed the drug, unless the payments have been specified in a protocol for the project which has been approved by the relevant national or local ethical committee. It is improper for doctors to accept payment in money or kind which could influence their professional assessment of the therapeutic value of a new drug."

17   Have you enclosed a specimen of written consent form?

        Yes

18   Is it your intention to inform the patient's G.P of his/her inclusion in the study?

        Yes

19a   Will patient medical records be examined by research member(s) outside the   employment   of   the
NHS?

        Yes. Psychologist

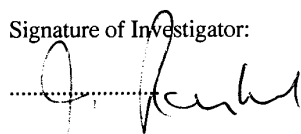19b   If yes above what steps will be taken to safeguard confidence?

        Clinician investigator will obtain honorary contract for patient contact.

The information supplied above is to the best of my knowledge and belief accurate. I understand my obligations and the rights of the patient, particularly the need to obtain freely given written informed consent.

Date of Submission: Signature of Investigator:

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To be completed by the Consultant in Charge or Head of Department

I have read through the study protocol and this form.
I hereby endorse this application with my approval:-

Signature: ....

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▇ CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	4.5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6,7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	8
	13b	For each group, losses and exclusions after randomization, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9,10
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

(Reprinted) JAMA, July 7, 2010—Vol 304, No. 1 **E1**

Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain

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Word count: 3,357

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ABSTRACT

Objective

This study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity.

Design

Randomised, double blind, controlled, parallel group trial.

Setting

Department of Pain Management, Russells Hall Hospital, Dudley, United Kingdom.

Participants

Twenty-four non-cancer pain patients implanted with morphine reservoirs were assessed for eligibility.

Interventions

Participants were randomly allocated to one of two parallel groups in which one of the groups had no change in morphine dose and the other group had a small reduction (20%) in dosage every week during a 10-week follow-up.

Outcome

Primary outcomes were visual analogue scale (VAS) pain score change and withdrawal from study due to lack of efficacy.

Results

Nine of the patients assessed for eligibility declined to participate in the study. Fifteen patients were randomised to control (n=5) or intervention (n=10) and included in an intention-to-treat analysis. Due to worsening of pain, seven patients withdrew from the study prematurely. None knew prior to withdrawal which arm of the study they were in, but all turned out to be in the dose reduction arm. Calculation of drop-out rate between groups indicated a significant statistical difference (p=0.026) and recruitment was ceased. VAS change between baseline and last observation was smaller in the control group (Mdn=11) than in the intervention group (Mdn=30.5), although not statistically significant, Z=-1.839, p=0.070, r=-0.47. Within groups, VAS was significantly lower at baseline (Mdn=49.5) than at last observation (Mdn=77.5) for the reduction group, Z=-2.805, p=0.002, r=-0.627 but not for the control group (p=0.188).

Conclusion

This double blind RCT of chronic intrathecal morphine administration suggests effectiveness of this therapy for the management of chronic non-cancer pain. However, due to small number of patients completing the study (n=8) further studies are warranted.

2

Trial registration

International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

INTRODUCTION

Opioid receptors were identified in the spinal cord in 1973.[1] Subsequent animal studies demonstrated that intrathecal opioids produce powerful and highly selective analgesia.[2] Intrathecal opioids exert their analgesic effect pre and post synaptically by reducing neurotransmitter release and by hyperpolarising the membranes of neurones in the dorsal horn, thus inhibiting pain transmission.[3]

The technique of intrathecal drug delivery is based on the principle that effective analgesia can be achieved by the action of some drugs at the dorsal horn and adequate concentrations cannot be achieved by systemic administration, or only by high systemic doses. Delivery of the drug by the intrathecal route is a means of achieving these enhanced therapeutic effects. The smaller doses needed for intrathecal administration also allow a reduction in side effects compared to systemic administration. Following the first clinical use of epidural [4] and intrathecal opioids,[5] Cousins used the expression 'selective spinal analgesia' to describe the phenomenon that spinally administered opioids could produce a specific analgesic effect with few motor, sensory or autonomic side effects.[6] It was subsequently demonstrated that the analgesic effect was, in the main, due to the uptake of the opioid directly into the spinal cord and cerebrospinal fluid.[3]

Key indications for intrathecal drug delivery systems are chronic pain unresponsive to curative medical or surgical measures and to more conservative palliative measures including systemic analgesics, physical therapies, psychological therapies, perineural injection procedures and nerve lesioning procedure. Pathologies for the pain are broad and only exclude psychogenic pains; they can be due to cancerous or non-malignant pathologies. Morphine is considered the 'gold standard' medication for intrathecal drug delivery systems because of its stability, receptor affinity and extensive experience of using the drug by this route.[7]

For chronic non-malignant pain it is strongly recommended that patients have a comprehensive psychological assessment [8] to: (i) assess possible concurrent psychopathology (e.g. severe affective disorder, body dysmorphia, procedural fears) that might impede successful implantation; and (ii) consider what additional individualised preparation might be advisable for the patient.[9] Cognitive behavioural therapy should not be excluded as a subsequent treatment

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option. It may ensure that the reduction in pain severity expected as a result of the ITDD system is capitalized upon by the development of reduced pain related behaviours and increased activity in a range of adaptive behaviours.

The first reservoir for intrathecal analgesic delivery was implanted in 1981,[10] and since then continuous intrathecal analgesia using opioids and other analgesics has become a recognized therapy for the management of severe and otherwise intractable chronic pain despite a lack of well-controlled studies. A three-year prospective study of intrathecal opioid treatment for chronic non-cancer pain showed that when patients with extremely severe pain problems are selected for intrathecal drug delivery, they are likely to improve with the therapy but their overall severity of pain and symptoms still remains high.[11] At least minimally clinical important changes in pain intensity were observed in 95% of participants in a recent study with a mean follow-up duration of 13 years.[12] Improvements were also observed in sensory and psychosocial outcomes.

Recent systematic reviews were unable to find randomised controlled trials (RCTs) evaluating the effectiveness of long-term intrathecal drug delivery systems (IDDS) for the management of chronic non-cancer pain.[13,14] Overall, the use of intrathecal opioid administration seems beneficial but the current available literature is too sparse to draw definite conclusions mainly due to the quality of the evidence. A systematic review of multiple well-designed RCTs is considered the highest level of evidence for the efficacy of a pain treatment, followed by a well-designed RCT of adequate size as the next best level of evidence.[15] To our knowledge there is only one such study of intrathecal opioids and that is confined to cancer pain.[16]

In the absence of strong supporting evidence for the use of intrathecal opioids for chronic non-cancer pain, the therapy must be balanced against its risks as procedure related complications have been reported to occur at a rate of 0.29 events per patient year and catheter related complications at a rate of 0.05 events per patient year.[17] Possible infections include meningitis, epidural abscess, pump pocket infection or pump reservoir infection. The rate of meningitis reported by studies ranged from 2.3% to 15.4% and for wound infections from 4.2% to 8.8%.[18] When considering only non-cancer pain studies, the percentage of patients with meningitis ranged from 0% to 4% and for wound infections, from 0% to 22%.[19] Furthermore, less common but serious events of permanent neurological injury can occur due to development of opioid associated granulomata. The incidence for this adverse event has been reported as 0.04% after one year, increasing to 1.15% after six years.[20] The management of the different

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adverse events is varied as some acute side-effects may resolve with time (e.g. nausea, vomiting, dizziness, or itching). Recommendations for aftercare, on-going care, prevention and management of potential complications and side-effects has been described.[8,18]

We had previously undertaken a prospective controlled study, of single dose morphine compared with saline in patients with chronic non-malignant pain and demonstrated spinal morphine to be efficacious in the short term for patients who respond to systemic morphine but in whom side effects have become intolerable.[21] The current study aimed to investigate the efficacy of intrathecal morphine in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity. Our primary outcome was visual analogue pain score change and withdrawal from study due to lack of efficacy.

METHODS

Study design and participants

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462). We conducted a single centre, double-blind, equal randomization [1:1], dose reduction, controlled, parallel group study. All subjects provided written informed consent. The original protocol anticipated using diamorphine, but between trial approval and trial commencement, practice changed to using morphine and the protocol was amended to reflect this.

Treatment strategies for the management of chronic pain start with the lowest risk and least invasive intervention and progress if a treatment is not effective. IDDS is a last-resort treatment to treat severe chronic pain because of their invasive nature, concerns about long-term opioid use, and the possible complications related to the procedure. IDDS is considered for use in patients with chronic non-cancer pain after more conventional treatments have failed (e.g. pharmacotherapy, transcutaneous electrical stimulation or in some cases spinal cord stimulation) and in those who respond to systemic opioids but the side effects have become intolerable. Patient suitability is also determined by a multidisciplinary team assessment that includes a clinical psychologist. A biopsychosocial history is performed, in which factors such as organic cause of pain, topography, duration of pain, pain intensity, coping strategies, social support, medico legal matters, history of anxiety and/or depression, previous treatments, and

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drug and/or alcohol abuse is taken into consideration. Where there is discrepancy across the clinical team of physician, physiotherapist, psychologist and specialist nurse, a case conference is set up to include the family physician, and other psychologists, physiotherapists and physicians not directly involved in intrathecal therapy.

Following multidisciplinary assessment all patients have an inpatient trial of intrathecal therapy prior to implantation. This is conducted by repeated bolus of morphine and saline in a single blind fashion.[21] Patients reporting greater than 50% relief with morphine and less with saline are selected for IDDS. Chronic dosing is extrapolated and titrated at refills (approximately two per month initially). A small increase in opioid dose may be necessary to maintain an adequate pain control. Recent observations indicate that significant differences cease following year 3 of therapy suggesting stability.[12] Additional intrathecal drugs were added if level of analgesia is inadequate as per polyanalgesic consensus conference algorithm.[22] Adjuvant intrathecal medication such as bupivacaine may contribute to achieve better pain control and to maintain low intrathecal morphine doses in cancer [23] and non-cancer patients.[24]

Eligible participants were adults aged 18 or over with implanted intrathecal reservoirs of programmable type (Synchromed, Medtronic Ltd) receiving intrathecal morphine for non-cancer pain and having had infusion for ≥ 12 months. Patients had reported a stable level of analgesia with the pump, based upon their attendance for pump refills at which dose did not change and they reported analgesia. In view of the need for weekly attendance during the study only those patients living within a short time journey from the hospital, with access to transport and limited co-morbidities were considered.

The pain nurse approached eligible patients for consent and patients were randomly assigned by computer generated randomization (PN) to one of two parallel groups in which one of the groups had no change in the morphine dose (control group) and the other group had a small reduction (20%) in the preceding week dose every week during participation in the study (intervention group). The allocation sequence was received in sequentially numbered, opaque and sealed envelopes to ensure that the sequence was concealed. Patients were unaware as to which group they were in, as the dose alteration or no change was conducted by telemetry with the screen not visible to the patient. The telemetry was conducted by a physician (JHR) who was the only investigator aware of the allocation. Pain scores and other outcome measures were collected by a researcher (RVD) blinded to the allocation of the patients.

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Outcome measures

Primary outcome measures were visual analogue scale (VAS) [25] score for pain and withdrawal from study. Secondary outcome measures were functional and psychological measures based on Oswestry Disability Index (ODI),[26] Hospital Anxiety and Depression scale (HAD)[27] and Coping Strategies Questionnaire (CSQ).[28] Subjects were evaluated at baseline and each week during participation in the study. VAS and ODI were collected on a weekly basis. HAD and CSQ were collected fortnightly.

Patients were asked to rate their average pain intensity during the previous week using a VAS. The VAS consists of a 100 mm straight line with anchors at its ends labelled as no pain and worst pain imaginable. The VAS is a recognised method for the assessment in variation of pain intensity.[25,29] Clinically important changes were classified in accordance with a consensus statement that established a 10-20% decrease as minimally important, ≥ 30% as moderately important and ≥ 50% as a substantial change.[30]

The ODI is used to assess the level of pain interference with various activities of daily living. The ODI is a valid measure of condition-specific disability.[31] The ODI consists of 10 items/activities with 6 levels (range 0-5). Scoring of this questionnaire was calculated as recommended by Fairbank and Pynsent.[31]

The HAD scale is a self-report rating scale of 14 items with 4 levels (range 0-3). This scale is used to screen for anxiety and depression (7 intermingled items for each subscale). The total score for each subscale is the sum of the respective seven items (ranging from 0–21). The HAD scale is considered a valid instrument for detecting states of anxiety and depression.[32]

The CSQ is a self-report instrument to assess active and passive coping skills of chronic pain patients.[33] The CSQ includes cognitive coping strategies (diverting attention, reinterpreting pain sensation, catastrophising, ignoring pain sensations, praying or hoping, coping self-statements), behavioural coping strategies (increasing activity level), and effectiveness ratings (control over pain, ability to decrease pain). Scores of these subscales result in 3 factors that account for 68% of the variance in questionnaire responses (cognitive coping and suppression, helplessness, diverting attention and praying). This questionnaire is a valid and reliable tool for chronic pain patient assessment.[28]

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Data analysis

An *a priori* power analysis based on previous open study data of reduction in VAS for pain with intrathecal therapy [21] computed a sample size of 24 (12 per group) would provide 80% power at the 5% significance level to detect a difference in the means of 1.2 standard deviations (unpaired t test) or a difference between the two proportions 20% and 80% (Fisher's Exact Test). The power analysis was based on a study which compared one group receiving morphine with one group receiving placebo (saline). The difference in means in the pilot study (5.1-0.91 = 4.19) was not used as the basis for the power calculation as the difference in the pilot study was likely to be larger than the difference observed in the current study where both groups received morphine. A difference in the means of 1.2 standard deviations was considered as a realistic estimate since we allowed for the effect to be much smaller than that observed in the pilot study (2.6 standard deviations if the standard deviations of 1.3 and 1.9 are pooled). Imputation methods were not used since the drop-out rate in the group randomised to have intrathecal dose reduction was 70%. This high drop-out percentage rate would bias the results regardless of the imputation technique employed. Therefore, we followed an intention-to-treat protocol; all subjects were included in the analysis and this was limited to within and between-group comparisons of baseline and final observation scores.

Kolmogorov-Smirnov test was performed to test normality of numerical data. The majority of the numerical data was not normally distributed and attempts to transform the data were unsuccessful. Therefore, differences between patient baseline characteristics were performed using the Mann-Whitney U test. Differences between baseline and last observation scores were evaluated using Wilcoxon Signed Ranks test. Categorical variables were investigated using Fisher's exact test. Data is reported as median (minimum-maximum). Statistical significance was judged at 5% level. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0, SPSS Inc., Chicago, IL, USA).

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RESULTS

Between 2006 and 2011, 24 patients were assessed for eligibility, nine declined to participate. Following inclusion in the study of 15 patients, it was observed that a high rate of patients withdrew from the research (Figure 1). Because of the large number of withdrawals, a first interim analysis was undertaken just beyond half way point which revealed that the withdrawals were all from the group randomised to have dose reduction. The drop-out rate in the group randomised to have intrathecal dose reduction was 70% and there were no drop-outs in the patients allocated to the control (no dose reduction) group. One subject left the study following week 1, three patients withdrew after week 2, two participants after week 5 and one patient after week 7. The intrathecal opioid dose in the patients that withdrew from the study was reduced from a median of 1.6 mg/day (0.625 – 5.5) to 1.15 mg/day (0.4 – 2.8) which corresponds to a decrease of 36% (20 - 79) in the intrathecal opioid dose. The reason for drop-out from the study was related with worsening of pain for all the participants. Calculation of drop-out rate between the groups indicated a significant statistical difference (p = 0.026). Recruitment ceased at that moment.

(Insert Figure 1/flow diagram here)

The patients recruited comprised 8 men (53.3%) and 7 women (46.7%) with a median age at the moment of enrolment in the study of 58 years (45-68). The median duration of IDDS therapy prior to participation in this study was 26 months (12-180). The pain syndrome was mechanical nociceptive caused by degenerative low back pain in 5 (33.3%) of the participants; visceral nociceptive due to post surgery abdominal pain in 1 (6.7%) patient and mixed nociceptive-neuropathic following failed back surgery syndrome in 9 (60%) subjects. The 5 patients in the control group comprised 2 with mechanical back pain and 3 with failed back surgery syndrome; the 10 in the intervention group comprised 3 with mechanical back pain, 6 with failed back surgery syndrome and 1 with post-surgery abdominal pain. All patients had been on systemic opioids prior to pump implantation and thereafter only took opioids intrathecally. The preparations differed and the equivalent oral morphine dose prior to implant ranged from 20 to 240mg morphine equivalent per day (Table 1 and 2).

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Table 1. Baseline characteristics of the patients according to randomization group

Characteristic	Control group (n = 5)	Intervention group (n = 10)	Test statistic	P
Age (years)	55 (45 - 59)	64 (52 - 68)	Z = -1.719	0.095
Gender (M/F)	4/1	4/6		0.282
Duration of therapy (months)	66 (22 - 88)	20.5 (12 - 180)	Z = -1.191	0.265
Pre-implant oral morphine dose mg/day	60 (20 - 120)	50 (40 - 240)	Z = -0.638	0.579
Morphine dose mg/day	4.625 (2.125 - 5.65)	1.612 (0.625 – 5.5)	Z = -2.205	0.028
Adjuvant intrathecal medication (Y/N)	4/1	5/5		0.580
Bupivacaine dose mg/day	3.190 (2.05 - 4.433)	2.050 (1.65 - 2.122)	Z = -1.715	0.111
Visual Analogue Scale	59 (0 - 69)	49.5 (10 - 64)	Z = -1.043	0.323
Oswestry Disability Questionnaire	54 (12 - 64)	55.85 (42 - 72)	Z = -0.677	0.529
Hospital Anxiety and Depression scale				
HAD anxiety	8 (2 - 16)	7.5 (1 - 12)	Z = -0.369	0.745
HAD depression	7 (2 - 11)	7.5 (2 - 15)	Z = -0.802	0.450
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	11.5 (0 - 31)	Z = -0.147	0.918
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.477	0.690
Catastrophising	7 (2 - 31)	22 (1 - 27)	Z = -0.147	0.911
Ignoring pain sensations	8 (3 - 21)	8 (0 - 28)	Z = -0.221	0.862
Praying or hoping	14 (2 - 26)	18.5 (0 - 30)	Z = -0.366	0.753
Coping self-statements	25 (15 - 30)	19 (2 - 32)	Z = -0.954	0.375
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.366	0.753
Control over pain	2 (1 - 5)	3 (1 - 4)	Z = -0.301	0.757
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -0.846	0.543
Cognitive coping and suppression	32 (18 - 70)	32.5 (6 - 83)	Z = -0.293	0.833
Helplessness	-7 (-14 - 10)	2 (-36 - 11)	Z = -0.806	0.458
Diverting attention and praying/hoping	26 (2 - 54)	31.5 (0 - 56)	Z = -0.440	0.698

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented *p* < 0.05

There were no statistically significant differences between the groups at baseline for age, gender, duration of therapy prior to study, adjuvant intrathecal medications, VAS, ODI, HAD scale and CSQ (Table 1). The intrathecal opioid dose administered at study entry was significantly higher in the control group (*Mdn* = 4.625) than in the intervention group (*Mdn* = 1.612), a chance finding, *U* = 7.00, *p* = 0.028, *r* = -0.57. A comparison of baseline scores between patients who completed the study and those that did not complete demonstrates non-

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significant differences for all the variables, including intrathecal dose administered at start of investigation (Table 2).

Table 2. Baseline characteristics of the patients according to completion of study

Characteristic	Complete (n = 8)	Incomplete (n = 7)	Test statistic	P
Age (years)	56.5 (45 - 68)	64 (53 - 66)	Z = -1.102	0.296
Gender (M/F)	6/2	2/5		0.132
Duration of therapy (months)	25 (15 - 88)	27 (12 - 180)	Z = -0.081	0.960
Pre-implant oral morphine dose mg/day	60 (20 - 120)	60 (40 - 240)	Z = -0.241	0.869
Morphine dose mg/day	3.065 (1.02 - 5.65)	1.6 (0.62 – 5.5)	Z = -1.273	0.232
Adjuvant intrathecal medication (Y/N)	5/3	4/3		1.000
Bupivacaine dose mg/day	2.5 (1.7 – 4.25)	2.085 (1.86-2.12)	Z = -0.735	0.556
Visual Analogue Scale	44.5 (0 - 69)	54 (23 - 64)	Z = -0.522	0.632
Oswestry Disability Index	53 (12 - 64)	57.7 (42 - 72)	Z = -1.222	0.244
Hospital Anxiety and Depression scale				
HAD anxiety	7 (2 - 16)	8 (1 - 12)	Z = -0.116	0.934
HAD depression	9 (2 - 15)	7 (2 - 12)	Z = -0.816	0.447
Coping Strategies Questionnaire				
Diverting attention	12 (0 - 29)	13 (0 - 31)	Z = -0.501	0.649
Reinterpreting pain sensation	0 (0 - 19)	3.5 (0 - 26)	Z = -0.466	0.714
Catastrophising	22 (2 - 31)	15 (1 - 27)	Z = -0.575	0.608
Ignoring pain sensations	8 (0 - 21)	8 (0 - 28)	Z = -0.215	0.861
Praying or hoping	15 (2 - 30)	18.5 (0 - 25)	Z = -0.358	0.760
Coping self-statements	24 (13 - 30)	19 (2 - 32)	Z = -0.358	0.755
Increasing activity level	16 (3 - 30)	13.5 (6 - 29)	Z = -0.143	0.916
Control over pain	2 (1 - 5)	3.5 (2 - 4)	Z = -1.101	0.317
Ability to decrease pain	2 (1 - 4)	3 (2 - 4)	Z = -1.050	0.386
Cognitive coping and suppression	32 (12 - 70)	32.5 (6 - 83)	Z = -0.000	1.000
Helplessness	-5 (-14 - 11)	0 (-36 - 10)	Z = -0.215	0.868
Diverting attention and praying/hoping	27 (2 - 54)	31.5 (0 - 56)	Z = -0.287	0.809

Median (minimum-maximum); gender and adjuvant IT medication were evaluated using Fisher's exact test, all other variables analysed using Mann-Whitney U test (Exact sig. (2-tailed)); statistical significance represented $p < 0.05$

The VAS change between baseline and last observation was lower in the control group (Mdn = 11) than in the intervention group (Mdn = 30.5), although not statistically significant, Z = -1.839, p = 0.070, r = -0.47 (Table 3). There were no statistically significant differences between the randomised groups in the changes detected for ODI, HAD scale anxiety and depression and all items of CSQ between baseline score and final observation.

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Table 3. Changes between baseline and last observation

	Control group (n = 5)	Intervention group (n = 10)	Test statistic	*P*
VAS	11 (-4 - 40)	30.5 (2 - 77)	*Z* = -1.839	0.070
ODI	12 (4 - 18)	6 (-2 - 30)	*Z* = -1.070	0.311
HAD anxiety	1 (-6 - 3)	0.5 (-3 - 5)	*Z* = -0.523	0.653
HAD depression	0 (-1 - 3)	0 (-3 - 6)	*Z* = -0.074	0.959

Median (minimum-maximum); variables analysed using Mann-Whitney U test (Exact sig. (2-tailed))

Within group comparisons were also carried out (Table 4). Statistically significant differences for VAS were observed between baseline and last observation in the group randomised to have dose reduction (intervention) but not in the control group (*p* = 0.188). The VAS was significantly lower at baseline (*Mdn* = 49.5) than at last observation (*Mdn* = 77.5) for the intervention group, *Z* = -2.805, *p* = 0.002, *r* = -0.627 (Figure 2). The ODI scores at baseline (*Mdn* = 55.85) were significantly lower than at last observation (*Mdn* = 68.40) for the group allocated to have dose reduction, *Z* = -2.201, *p* = 0.027, *r* = 0.492. No statistically significant differences were observed for the ODI in the control group (*p* = 0.063). There were no statistically significant changes detected for HAD scale anxiety and depression and all items of CSQ in either randomised group between baseline score and final observation.

Table 4. Within group analysis for VAS and ODI

		VAS	ODI
Control group (n = 5)	Baseline	59 (0 - 69)	54 (12 - 64)
	Last observation	70 (40 - 83)	64 (30 - 74)
	Test statistic	*Z* = -1.625	*Z* = -2.032
	P	0.188	0.063
Intervention group (n = 10)	Baseline	49.5 (10 - 64)	55.85 (42 - 72)
	Last observation	77.5 (57 - 100)	68 (48 - 84)
	Test statistic	*Z* = -2.805	*Z* = -2.201
	P	0.002	0.027

Median (minimum-maximum); variables analysed using Wilcoxon test (Exact sig. (2-tailed))

The calculation of clinical changes based on the VAS scores indicated non-significant clinical changes in 10% of the patients in the dose reduction group (intervention), minimally clinically important changes (≥10% and <30%) were observed in 20% of the participants randomised to this group, moderately important increase in pain (≥30% and <50%) in 40% of the subjects and substantially important increase in pain (≥50%) in 30% of the patients. For the group where the

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morphine dose remained the same (control), non-significant changes were observed in 40% of the sample, minimally clinically important changes (≥10% and <30%) in 40% of the participants and one patient (20%) had a clinically substantial increase in pain.

(Insert Figure 2 here)

DISCUSSION

This randomised controlled trial of intrathecal opioid therapy in chronic non-malignant pain has demonstrated differences in pain relief between dose reduction and dose maintenance. It lends support to the efficacy of this therapy, which until now has not been subject to controlled trials.

A power analysis indicated that 24 patients would need to be included in the study to obtain a power of 0.8; however, due to high number of withdrawals, we undertook an interim analysis in which we found that the withdrawals were all in the dose reduction arm. The attrition rate of 70% in the group randomised to have reduction also indicates that the treatment seems to be effective. Statistically significant differences between the arms were observed and the study was stopped. Although not statistically significant, the VAS change between baseline and last observation was lower in the control group than in the reduction group. Within group VAS and ODI differences were statistically significant between baseline and last observation for the treatment arms with statistically significant greater pain and worsened disability in the dose reduction arm. Clinically important changes indicating an increase in pain intensity were observed in 90% of the patients randomised to dose reduction (intervention). These changes were moderately important (≥30% and <50%) in 40% of the patients and substantially important (≥50%) in 30% of the participants.

Significant differences between groups at enrolment were observed for morphine dose. The dose maintenance group (control) were found to have a significantly higher starting opioid dose. This mirrored the statistically insignificant trend towards longer duration of intrathecal therapy. It is possible that this group had greater levels of pain than the intervention group for the same dose of opioid and/or that with longer duration of therapy, the dose had increased with time, as a small increase in opioid dose may be necessary to maintain an adequate pain control and recent observations from our unit indicate that significant differences cease following year 3 of therapy suggesting stability.[12] When dose escalation occurs, it is usually due to tolerance, progress of the disease [34] or opioid induced hyperalgesia.[35]

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All subjects had stable levels of opioid delivery as evidenced by no change in delivered dose at recent refills before investigation and all reported analgesia with comparable pain scores (VAS). In using percentage dose reduction in this study, we anticipated overcoming a potential bias from this. Furthermore, no significant differences were observed at enrollment between those who completed the study and those who withdrew before completion, indicating that the initial opioid dose did not impact on drop-out rate. We had purposely chosen a small decrease of dose (20%) to avoid the patients suffering any withdrawal symptoms and none occurred. This parallels the experience of Rauck and colleagues in a study of opiate reduction within the context of investigating ziconotide.[36] In this study there was a 3 week weaning period prior to entering the trial and thus the weekly reduction in IT opioids would therefore be approximate to 30%. The weaning process was successful in 92.9% of the patients, only 14 dropped out due to inability to tolerate withdrawal, adverse events, noncompliance or patients request.

This study has recognised weaknesses of small sample size and being conducted in a single centre. The sample size was inferior to the 24 patients indicated by the a priori power analysis as the study was stopped when an interim analysis was conducted due to large number of drop-outs and revealed significant differences for withdrawals between groups. There was an imbalance in the number of patients in each group. The patients were randomised as a single block of 24, thus ensuring that in a sample of 24 there would be 12 in each group. Randomisation of smaller blocks would ensure that there were equal numbers in each group for smaller sample sizes as well (e.g. if we had used a block size of 6, we would have had equal numbers in each group after 6, 12, 18 and 24 patients had been randomised). With our single block of 24, the chance of getting a split as uneven as 10 and 5 after 15 patients was about 9%. This RCT was conducted in a single centre. Selection for therapy followed the national guidelines;[8] however, their interpretation may vary in clinical practice even within the same country in the psychosocial domains of pain. Dose titration strategies may differ across treatment centres. Different centres have reported average doses of 4.7 mg/day at an average of 3.4 years,[37] 7.42 mg/day at 29.14 months,[38] 9.6 mg/day at year 1 [39] and 12.2 mg/day at year 3.[40] This may lead to different levels of opioid delivery for which the sensitivity to dose reduction may differ.

The strengths of this study were not looking in the period following intrathecal drug delivery implantation because we considered that this period is confounded by need for dose titration

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and the non-specific psychological effects of a major intervention. In investigating patients with intrathecal delivery for a minimum of 12 months, we have been able to focus on evaluation of long term efficacy of intrathecal opioid therapy. To our knowledge this is the first randomised double-blind controlled study of this therapy in non-cancer pain. The findings of our randomised controlled trial suggest the efficacy of intrathecal morphine for the management of chronic non-cancer pain. Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction. In the light of these results, investigation of different populations and larger cohorts are recommended.

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Figure legends

Figure 1. Flow chart of patient participation

Figure 2. Individual visual analogue scale scores at baseline and final observation for control group (n=5) and reduction group (n=10).

ARTICLE SUMMARY

Article focus

- Recent systematic reviews were unable to find randomised controlled trials evaluating the effectiveness of long-term intrathecal drug delivery systems for the management of chronic non-cancer pain.

- We aimed to investigate if a small decrease in the intrathecal morphine dose leads to an increase in reported pain scores in chronic non-cancer pain patients undertaking long-term intrathecal morphine.

- The randomised controlled trial design would allow to investigate the long-term efficacy of intrathecal morphine delivery.

Key messages

- Statistically and clinically significant increases in pain intensity were observed for patients randomised to have intrathecal morphine dose reduction.

- The findings of this study suggest the efficacy of intrathecal morphine delivery for the management of chronic non-cancer pain.

Strengths and limitations of this study

- To our knowledge, this is the first randomised controlled trial investigating the efficacy of intrathecal drug delivery systems for the management of chronic non-cancer pain.

- By investigating patients with intrathecal delivery for a minimum of 12 months this study is not confounded by need for dose titration and the non-specific psychological effects of a major intervention.

- Limitations of this study include small sample size and being conducted in a single centre.

Acknowledgments

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Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

JHR designed and was responsible for the conception of the trial. JHR, RVD, JLS, PN, GDK have made substantial contributions to (1) the acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

The study was approved by the Birmingham and Black Country Research Ethics Committee (REC/35/02/JUN) and registered with the International Standard Randomised Controlled Trials Centre (ISRCTN 33733462).

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