Comparison of the effects of intermittent boluses to simple continuous infusion on patients' global perceived effect in intrathecal therapy for pain: a randomised double blind crossover study

Sam Eldabe, MD [1] Rui V. Duarte, PhD [2] Grace Madzinga, [1] Alan M. Batterham, PhD [3] Morag E. Brookes, MSc [1] Ashish P.Gulve, MD [1] Christophe Perruchoud, MD [4] Jon H. Raphael, MD [5] David Lorenzana, MD [6] Eric Buchser, MD [4]

1. Department of Pain and Anaesthesia, The James Cook University Hospital, Middlesbrough, UK

2. College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

3. Health and Social Care Institute, Teesside University, Middlesbrough, UK

4. Anaesthesia and Pain Management Department, EHC-Hôpital de Morges, Morges, Switzerland

5. Department of Pain Management, Russells Hall Hospital, Dudley, UK

6. Anaesthesia and Pain Management Department, Kantonsspital Luzern, Luzern, Switzerland

Corresponding author: Sam Eldabe, Department of Pain and Anaesthesia, The James Cook University Hospital, Cheriton House, Marton Road, Middlesbrough TS4 3BW, UK.

Email: seldabe@mac.com; Telephone: +44 (0) 164 228 2417

Running title: Intrathecal bolus vs continuous RCT

ABSTRACT

Objective: Intrathecal drug delivery (ITDD) is commonly used for intractable pain management. A paucity of good quality studies in chronic non-cancer patients and concerns over increased dosages has focused interest on different modes of administration. The aim of this international multicentre randomised double-blind crossover trial was to compare the efficacy of the same daily dose of drugs administered by intermittent boluses versus simple continuous infusion.

Methods: Eligible patients implanted with a programmable ITDD device were randomised to receive two weeks of either intermittent boluses or a simple continuous flow in period 1, followed by a crossover to the alternative mode of administration. The primary outcome measure was the Patients' Global Impression of Change (PGIC) scale.

Results: The mean proportion of positive responders (at least "minimally improved") was 38.4% in the Continuous condition versus 37.3% in the Bolus (difference in proportions = 1.1%; 95% CI, -21.8 to 24.0%; P=0.93). The mean PGIC in the Continuous condition was 3.8 versus 3.9 in the Bolus (mean difference = -0.1; -0.6 to 0.4; P=0.72). Exploratory analyses revealed a tendency for the mean proportion of positive responders to be higher at low vs. high flow rates for both bolus and continuous administrations. Two patients were withdrawn from the study due to adverse events during the Bolus phase: both with symptoms of increased pain, and one patient with additional symptoms of numbness and urinary retention.

Conclusion: The mean PGIC and proportion of positive responders was not substantially different after intermittent bolus versus continuous administration.

INTRODUCTION

The use of implanted devices for the intrathecal administration of drugs to relieve intractable pain has been practiced for nearly four decades [1]. The advantage of the intrathecal route is that, compared to systemic administration, an equivalent or better analgesic effect can be obtained with lower doses and therefore less severe side effects [2]. In addition, the direct access to the intrathecal space allows the use of drugs that cannot be administered by another route because of either systemic inactivation or inability to cross the blood brain barrier. Yet, despite increasing popularity, there is a paucity of high quality clinical studies, resulting in an ongoing controversy regarding the efficacy of intrathecal drug delivery (ITDD). More recently, clinicians have become interested in the influence of the flow profile on the treatment efficacy. Two blinded randomised controlled studies have shown that for a given dose, changing the daily flow rate did not significantly affect the clinical effect whether in patients with severe spasticity [3] or intractable pain [4]. An earlier clinical observation suggested that a small dose of bupivacaine given as a "fast" bolus produces better analgesia than a large dose given continuously (slowly) [5]. This is consistent with the finding of a previous double-blinded RCT that showed no benefit of adding bupivacaine to IT opioids administered as a continuous infusion, although the maximum daily dose of bupivacaine in this study was 8 mg/day compared to an average daily dose of 10 mg/day in other studies that demonstrated efficacy of adding bupivacaine to IT opioids [6].

Animal experiments conducted using flows similar to those delivered by programmable intrathecal infusion device have shown that intrathecal drug distribution into the cerebrospinal fluid (CSF) and spinal cord is limited when (low) clinically used infusion rates are utilised [7]. Increasing the flow rate from 20 microl/hr to 1000 microl/hr and the administration of the drugs as bolus resulted in a wider distribution of the study drugs baclofen and bupivacaine in the CSF and spinal cord parenchyma. The findings were the same regardless of the drug used. The author concluded that the position of the catheter tip is crucial when drugs are administered by slow continuous flow and that continuous infusions are associated with a higher risk of intrathecal granulomas, presumably because

the spinal cord and the meninges are exposed to higher drug concentrations. It has been suggested that use of the lowest effective dose and concentration of intrathecal opioids, intermittent bolus dosing, and adjuvant therapy with nonopioid analgesic medications may all prevent granuloma formation [8-10].

The aim of this study was to compare the efficacy of the same daily dose of drugs administered by intermittent boluses compared to simple continuous infusion on the Patients' Global Impression of Change (PGIC) scale. We postulate that administration of the same drugs by intermittent boluses will result in wider drug spread in the CSF and spinal cord parenchyma resulting in better analgesia.

METHODS

Study design

The study is an international multicentre randomised double blind crossover study. Two different modes of administration were evaluated, (1) the usual daily dose fractionated into 6 intermittent boluses and (2) the same dose administered as a simple continuous flow. Each flow pattern was maintained for two weeks in a double blind randomised crossover design. Safety and efficacy were evaluated by means of patient and assessor-based evaluations. Recruitment took place in two English centres (The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust; Russells Hall Hospital, Dudley Group of Hospitals NHS Foundation Trust) and two Swiss centres (EHC-Hôpital De Morges; Luzerner Kantonsspital).

The study was reviewed and approved by the ethics committee NRES Committee East Midlands – Northampton, reference: 10/H0402/54. The study was registered with ISRCTN61628624. All patients provided written informed consent prior to randomisation.

Study population

Patients were eligible for inclusion if they were 18 years of age or older, implanted with a programmable ITDD device for the management of non-cancer pain and having achieved

stable pain relief on a continuous flow. In addition, all eligible patients would be receiving one of morphine, clonidine or bupivacaine in isolation or a combination of any two of these intrathecal medications.

Exclusions included the use of a non-programmable ITDD pump, a patient-controlled mode (PTM device) or other bolus mode modality, patients receiving intrathecal ziconotide, patients with poor cognitive ability, severe limitation in function or mobility and refusing to participate in the study.

In this study all patients were implanted with a SynchroMed®II pump (Medtronic, Minneapolis USA).

Interventions

Intermittent Boluses Group (IB)

Subjects randomised to receive intermittent boluses underwent pump programming by the unblinded investigator in order to deliver a minimum background infusion rate of 48mcl/day as a continuous background infusion (pump programming does not allow for intermittent boluses alone). The remainder of the total daily dose was fractionated into six intermittent maximum speed (delivered over the shortest time period allowable by the ITDD) boluses delivered automatically at 4-hourly intervals. The total daily dose remained unchanged, i.e. was the same as before entering the study.

Continuous Infusion Group (CI)

Patients randomised to simple continuous infusion continued to receive the same dose of drugs at the same flow rate.

Study procedure

Eligible patients were randomised sequentially to receive either intermittent boluses or continuous infusion in a 1:1 ratio using a central randomisation system. The randomisation sequence was prepared by the trial statistician (AB) and allocation concealment maintained

until completion of baseline data recording. At this time the allocation of the patient was revealed by e-mail to the (blinded) study coordinator.

The clinical team was split into two groups: the unblinded team, which provided the clinical care for the patients, and the blinded team, which was responsible for study data collection. These groups were strictly adhered to and no crossover of clinical staff occurred.

Programming of the intermittent boluses takes considerably longer time than simple continuous infusion and patients would be aware of this. To aid the blinding of the patient and blinded clinical team members, the programming took place in a separate room from the patient. After a period of approximately 15 minutes the unblinded clinical team member returned to the patient to update the intrathecal pump.

To ensure patients' safety during the trial phases of intermittent bolus (IB) and continuous infusion (CI), the concentration and dosing ranges for the intrathecal medications were carefully considered. The safe maximum daily doses for both the IB and CI groups were as follows:

- Morphine sulphate solution (preservative free) was administered at a maximum concentration of 40 mg/ml and at a maximum total daily dose of 10 mg/day;
- Clonidine hydrochloride was given at a maximum concentration of 2000 mcg/ml and a maximum total daily dose of 500 mcg/day;
- Bupivacaine hydrochloride was given at a maximum concentration of 30 mg/ml and a maximum total daily dose of 15mg/day.

Following pump programming patients were observed in a clinical area for 5 hours with 2 hourly vital signs and reported side effects were noted. The patients were contacted the day after the programming to either IB or CI to ascertain if any adverse events had occurred.

Each group received intermittent boluses or continuous infusion for a period of two weeks. A two-week period was deemed appropriate as it allowed for one week of stabilisation, with the outcomes being collected during the second week. Subjects initially randomised to group IB would crossover for a two-week period to group CI and vice versa. At the end of the study,

patients were asked whether they preferred, the initial or the second programming; the ITDD was then programmed according to their choice. If patients could not choose between the two programmes, a continuous infusion was programmed.

Outcome measures

The study primary outcome parameter was the PGIC [11]. The PGIC assesses the patient's self-rated overall change since the start of the study in a seven-point Likert scale. Patients rate their change as very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. The PGIC was completed at the end of each two-week period. The PGIC is a recommended core outcome measure of global improvement with treatment for use in chronic pain clinical trials [12].

Secondary outcomes included: pain assessed using a 100 mm visual analogue scale (VAS) ranging from 0 (no pain) to 100 (worst possible pain) collected by diary for five days prior to each visit [13], health-related quality-of-life using the EQ-5D-3L [14], adverse events and patient programme preference. We also asked the blinded study nurse to guess the therapy group between IB and CI to test the strength of the blinding (observer guess). VAS and EQ-5D-3L were collected at baseline (pre-randomisation), and at the end of each two-week period. Adverse events could be reported at any time during the study period. Patient programme preference and observer guess of the group were assessed at the end of the study.

Data analysis

The sample size estimation is linked directly to the analysis strategy, and was conducted using SAS® statistical software (Version 9.1, SAS Institute Inc., Cary, NC, USA) according to procedures outlined by Senn [15]. We defined the minimum clinically important difference (MCID) for the primary outcome – the PGIC scale - as a treatment effect (between-treatment difference) of half a standard deviation (SD). An effect size of 0.5 SDs is regarded as a good indication of the MCID for patient reported outcomes of this type. Indeed, this effect size was

found to be the mean MCID in a review [16], with the authors noting the remarkable consistency of this MCID across various methodologies and clinical conditions. With 2P=0.05 and 80% power the required sample size was 34 patients.

For the primary outcome of PGIC we performed two analyses: a responder analysis [17] and an analysis of PGIC as a continuous variable. For the former, a responder was defined as a patient reporting at least 'minimally improved' on the 7-point scale (i.e. a score of 1, 2, or 3). The PGIC as a continuous variable and the secondary outcomes (pain VAS, EQ-5D index, EQ VAS) were analysed using a conventional within-subjects model, accounting for the period effect. All analyses were conducted using Stata statistical software (v. 13.1; Stata Corp. College Station, Texas, USA). Patients with missing outcome data for one of the two periods were included in the analysis via application of a generalised linear mixed model using restricted maximum likelihood [18].

In a secondary analysis, we explored the effect of flow rate on both the primary outcome (responder analysis) and pain VAS via a flow rate × treatment interaction term. All mean effects are presented with 95% confidence intervals. Treatment effects were estimated at the 10th (3.1 mcl/hour) and 90th (18.5 mcl/hour) centiles for flow rate.

RESULTS

Study enrolment, allocation to the IB and CI groups, and follow-up of study participants are summarised in the flow diagram shown in Figure 1. Forty-six patients were screened and a total of 32 patients were randomised (IB group: 16; CI group: 16). Patient data at baseline is presented in Table 1. The median (IQR) for bolus percentage of total daily dose was 10.0 (7.7 to 13.7)%.
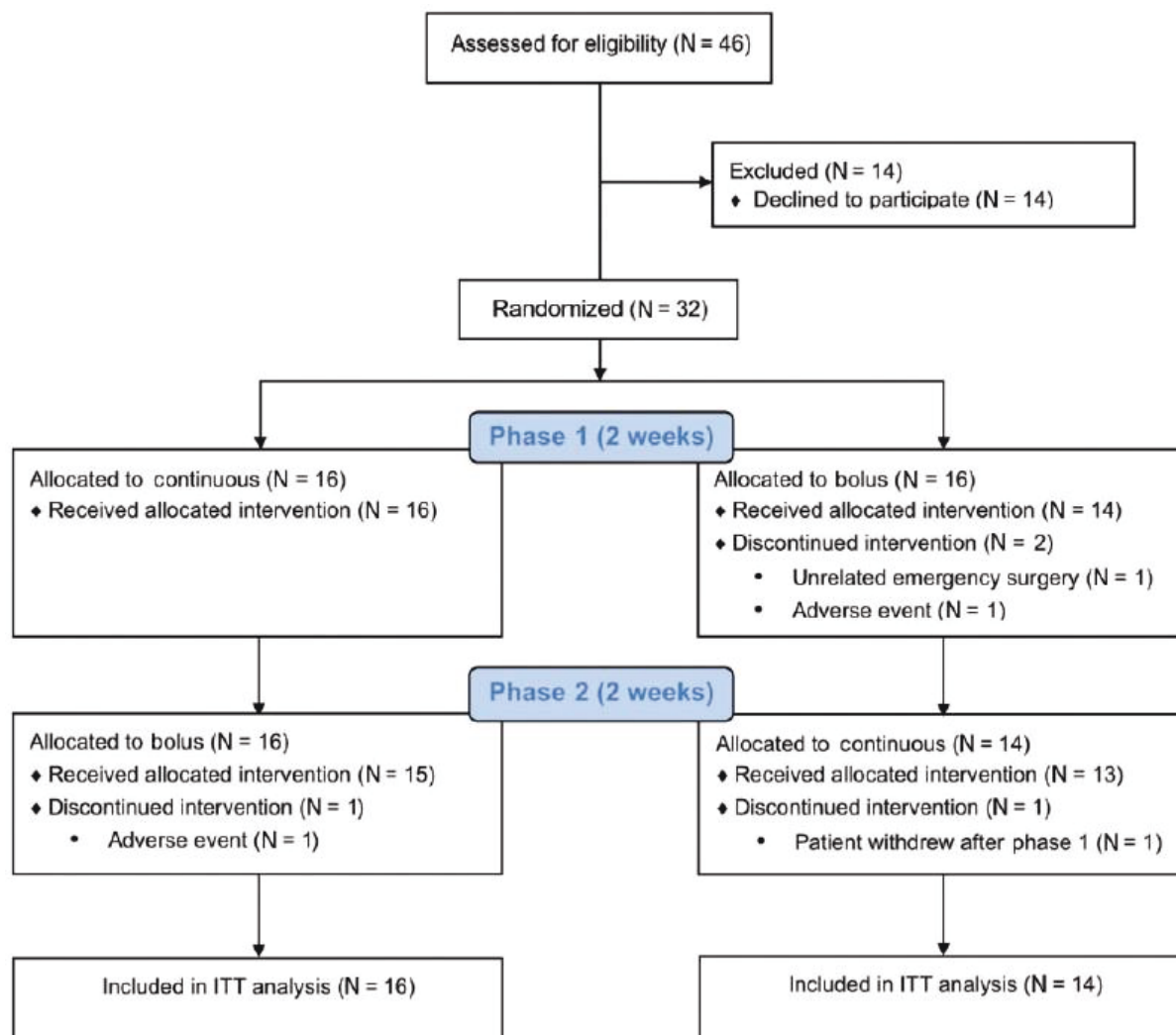
Figure 1 CONSORT flow diagram

Primary Outcome

Twenty-eight patients completed both bolus and continuous treatments. A further two

patients completed one of the two periods and were included in the analysis, as their data

help recover some of the missing within-subject information from the between-subject

information. The intention-to-treat analysis is therefore based on 30/32 patients.

The estimated mean proportion of positive responders to treatment was 38.4% in the

Continuous condition versus 37.3% in the Bolus. The difference in proportions (Continuous-

Bolus) was therefore 1.1% (95% CI, -21.8 to 24.0%; P=0.93). As a continuous variable, the

mean PGIC in the Continuous condition was 3.8 versus 3.9 in the Bolus. The mean

difference was -0.1 (-0.6 to 0.4; P=0.72).

Table 1. Patient characteristics at baseline (N=32 unless stated)

Variable	
Sex (M: F)	18: 14
Age (years)	55.3 (9.9)
Pain VAS (mm) [n=27]	49 (20)
EQ-5D index (median [IQR])	0.390 (0.072, 0.620)
EQ VAS (mm)	52 (19)
Morphine dose (mg/day) [n=23]	2.6 (1.7)
Bupivacaine dose (mg/day) [n=10]	3.8 (2.2)
Clonidine dose (mcg/day) [n=16]	164.8 (169.4)
Flow rate (mcl/hr)	11 (9)
Catheter tip position [n=27]	
Thoracic level (T10 to T12)	16 (59%)
Thoracic level (other)	3 (11%)
Lumbar level	8 (30%)

Data are mean (SD) unless stated. IQR, interquartile range.

Secondary Outcomes

Pain (VAS) and health-related quality-of-life (EQ-5D-3L)

Secondary outcome results for pain using the VAS and health-related quality-of-life using the

EQ-5D-3L are shown in Table 2. No substantial differences between treatments were

observed for the secondary outcomes.

Table 2. Treatment effects on secondary outcomes

Outcome	Continuous mean	Bolus mean	Difference (95% CI)
Pain VAS (mm)	47.9	49.2	-1.3 (-4.9 to 2.3)
EQ-5D index	0.385	0.388	-0.003 (-0.100 to 0.094)
EQ VAS (mm)	49.1	50.2	-1.1 (-6.3 to 4.1)

Patient Preferences

Of the 28 patients completing both bolus and continuous treatments, 14 (50%) expressed a preference for Continuous, 12 (43%) for Bolus, and 2 (7%) had no preference.

Observers guess of the group

Observer guess of the group was recorded for 26 patients that completed both bolus and continuous treatments. The observers guessed the group sequence correctly for 65% (17/26) of the patients (95% CI, 47% to 84%; P=0.06, against a hypothesised proportion of 50%).

Effect of flow rate

The Treatment × Flow rate interactions (Table 3) reveal that the mean proportion of positive responders (at least slightly improved on the PGIC) was greater at low flow rates within each treatment condition, with considerable uncertainty in the estimates revealed by the width of the confidence intervals. However, there was no substantial effect of flow rate on the bolus vs. continuous comparison. Similarly, pain is greater on average at higher vs. lower flow rates but with no substantial difference between treatments (Table 4).

Table 3. Interaction of flow rate with treatment effect: Estimated proportion of responders on the Patient Global Impression of Change (%)

Flow rate	Bolus	Continuous	Difference (95% CI)
3.1 mcl/hour	49.6	48.2	1.4 (-29.2 to 31.9)
18.5 mcl/hour	20.4	25.4	-5.0 (-40.0 to 30.0)
Difference between flow rates by treatment	29.1 (-9.1 to 67.3)	22.7 (-15.8 to 61.3)	

Table 4. Interaction of flow rate with treatment effect: Effect on Pain VAS

Flow rate	Bolus	Continuous	Difference (95% CI)
3.1 mcl/hour	43.2	41.6	1.6 (-4.2 to 7.5)
18.5 mcl/hour	57.1	56.4	0.7 (-7.8 to 9.1)
Difference between flow rates by treatment	-13.9 (-33.9 to 6.2)	-14.8 (-32.4 to 2.7)	

Adverse events

A total of 16 adverse events during bolus infusion and 12 during continuous infusion, potentially related with the treatment, were recorded during the study period (Table 5). One patient withdrew during the Bolus phase because of an emergency surgery for iliac aneurism (unrelated to the study) and one patient withdrew after initial programming (no reason provided). Two patients were withdrawn from the study due to adverse events during the Bolus phase. The patients presented with symptoms of increased pain, and one of the patients also presented with numbness and urinary retention. One of the patients was receiving morphine 5mg/day and clonidine 125 mcg/day at a flow rate of 10.42 mcl/hr, and the other patient morphine 2.3 mg/day and clonidine 17.9 mcg/day at a flow rate of 4.17 mcl/hr. Both patients were programmed to continuous infusion and made a full recovery following discontinuation of the study.

Table 5. Adverse events reported after each treatment phase

Adverse event	Bolus (N=32)	Continuous (N=32)
Numbness	4 (13)	0
Burning sensations	1 (3)	0
Increased pain	4 (13)	4 (13)
Nausea & vomiting	2 (6)	3 (9)
Headache	3 (9)	2 (6)
Hypertension	1 (3)	1 (3)
Urinary retention	1 (3)	0
Sweating	0	2 (6)
Other (unrelated)	5 (16)	1 (3)

Numbers represent N (%).

DISCUSSION

This international multicentre randomised double blind crossover trial is the first study powered to detect differences between bolus and continuous intrathecal administrations. No substantial differences between treatments for the primary and secondary outcomes were observed. This finding is in contrast with previous studies reporting improvements in patients' pain perception using intrathecal bolus administration [5,19]. Indeed, Buchser and colleagues [5] observed a patient who did not respond to a significant dose of bupivacaine

added to a continuous administration of morphine and clonidine but reported a reduction on the VAS from 70mm to less than 20mm following a bolus of 0.5 mg of bupivacaine. Recently, a small (n=10) randomised double blind crossover trial reported that patients receiving 40% of the daily dose as four boluses and the remaining 60% as a slow and constant background infusion obtained statistically significant decrease in pain scores when compared to continuous infusion [19]. A placebo effect cannot be excluded as a reason for this finding. Although the study claims that the patients were blinded to treatment administration, it is not clear how the programming of the pumps was performed. The patients would be aware of the time required to programme a continuous infusion and would notice a longer duration to reprogram the pump. Furthermore, responders to bolus administration tended to have lower pain scores in the first week of treatment a trend that was not statistically significant but may also suggest a placebo effect.

The CSF has limited capacity to distribute intrathecal morphine, baclofen, and bupivacaine away from the catheter tip [7,20]. It has been demonstrated that higher flow rates and bolus administration leads to a wider dispersion of intrathecal bupivacaine and baclofen [7]. However, the bolus / infusion ratio used in the Bernards study was increased 50 fold to a much higher rate (1000 microL/hr over five minutes every hour for eight hours) than what could be used in our patient group. An assessment of a similarly substantially different speed of delivery between continuous infusion and bolus could shed some light into possible differences in effect of the modes of administration, although it may not be feasible with current intrathecal pump technology. Bernards also observed that at 1000 microL/hr there is no difference in dispersion between continuous infusion and hourly boluses of 1000 microL which may explain the absence of differences in the current study between continuous infusion and bolus infusion for the same amount of the drug. Drug distribution in the CSF has also been found to be affected by body position [21]. Patients for this trial were excluded if they had severe limitation in function and mobility, which could have limited the drug distribution during daytime and subsequent patient-reported outcomes.

Catheter tip positioning and flow rate used are important factors to consider when trialling patients for ITDD. However, several patients that respond to the trial period then fail to obtain good pain relief following implantation of the pump requiring adjustments to the intrathecal medication. This may occur because the trial is usually performed using a bolus dose and following implantation the administration mode is changed to a continuous infusion. The drug distribution during continuous infusion may not be sufficient to produce therapeutic drug concentrations in spinal cord segments distant from the catheter tip [20]. The use of higher flow rates and consequent wider dispersion of the drugs, may lead to an insufficient drug concentration in the appropriate spinal cord segments resulting in increase in pain severity and decrease in EQ-5D index scores [3,4]. Adequate or inadequate placement of the catheter tip may help to explain why studies investigating changes in flow rate or bolus administration may have failed to observe significant results. Additionally, change in response after implantation could in part be caused by a placebo effect during the trial or patient increased expectations based on response during the trial period.

In our study there was no substantial effect of flow rate on the Bolus vs. Continuous infusions with differences between treatments being trivial at both low and high flow rates. However, mean differences between flow rates within each treatment condition were substantial, with a larger proportion of responders on the PGIC and lower pain ratings at low vs. high flow rates. The comparisons between low and high flow rates within each treatment condition are not statistically significant, but the investigations of interaction between flow rates with treatment effects were exploratory, as this study had low power to detect small, clinically relevant interactions. There is good evidence of a substantial main effect for flow rate that needs to be confirmed in a larger definitive study. We chose the PGIC as a primary outcome measure for this study rather than the VAS as the PGIC allows the patient the ability to express a balanced view on both pain relief and side effects, whereas the VAS only addresses pain relief. It is therefore possible that the trend for an effect for low flow rate may well be related to a smaller impact of side effects in lower flow group rather than improved pain scores in the PGIC. The device used in the study mandated a minimal background flow

rate of 48mcl/day, thereby imposing a greater restriction on bolus size in patients with lower flow rates. It is possible that such a restriction has led to a lower side effect rate and an accompanying improvement in PGIC in this group.

The observers guessed the group sequence correctly for 65% (17/26) of the patients. This rate of correct guesses was mainly due to observers being able to correctly interpret episodes related to medication side effects, i.e. sensory and motor changes resulting from boluses of bupivacaine and nausea related to opioids.

The main strengths of this study were its international multicentre randomised double blind crossover trial design using the patients as their own controls. However, there are some limitations that merit mention. A small number of patients were included, although the study was powered to detect a minimum clinically important difference for the PGIC. The use of daily activity monitoring or alternative physical function measures could have contributed to capture changes occurring due to modifications in the mode of intrathecal administration. The drugs used were heterogeneous as patients were receiving different drug combinations. Drug distribution within the CSF is affected by baricity [21]. The assessment of bolus infusion in patients using a single drug (e.g. baclofen) would allow a more objective assessment of treatment effect. Patients with a PTM device were not eligible for participation in this study as the bolus administration was scheduled; it is possible that by being able to control the timings of the boluses, participants in the study could have presented improved outcomes. Primary outcome data were missing from one period for two patients (one for Bolus and one Continuous) and from both periods for a further two patients. To explore the potential impact of these missing data, we conducted a simple 'extreme-case' sensitivity analysis favouring the continuous treatment (the treatment with the larger mean proportion of responders). This approach involved the assumption of a beneficial response for the three missing Continuous treatment periods and a non-beneficial response for the three missing Bolus treatment periods. The estimated mean proportion of positive responders to treatment of 43.8% in the Continuous condition versus 34.4% in the Bolus. The difference in proportions (Continuous-Bolus) was therefore 9.4% (95% CI, -12.7 to 31.4%; P=0.39). The fact that the difference

between treatments in the proportion of responders remains trivial in the sensitivity analysis shows that the primary analysis is robust in the face of a small proportion of missing data. In conclusion, there were no substantial differences in a continuous versus a bolus infusion on PGIC, either as a proportion of positive responders to treatment or as a continuous variable. No substantial differences were observed for the secondary outcomes. Due to the heterogeneity of drug combinations that were used in the patients included in this study and the potential effect of baricity on drug distribution, it would be important to investigate the effect of bolus administration in a patient population receiving a single intrathecal drug. Although the study had not been powered for this purpose, an exploratory analysis indicated a trend towards a greater proportion of positive responders (improved PGIC) and lower pain scores with low flow rates. This finding merits further investigation.

References

1] Onofrio BM, Yaksh TL, Arnold PG. Continuous low-dose intrathecal morphine administration in the treatment of chronic pain of malignant origin. *Mayo Clin Proc* 1981; 56: 516-520.

[2] Smith TJ, Coyne PJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, Buchser E, Català E, Bryce DA, Cousins M, Pool GE. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). *Ann Oncol* 2005; 16: 825-33.

[3] van der Plas AA, Marinus J, Eldabe S, Buchser E, van Hilten JJ. The lack of efficacy of different infusion rates of intrathecal baclofen in complex regional pain syndrome: a randomized, double-blind, crossover study. *Pain Med* 2011; 12: 459-65.

[4] Perruchoud C, Eldabe S, Durrer A, Bovy M, Brookes M, Madzinga G, Garner F, Batterham AM, Menoud C, Jacobs M, Gulve A, Buchser E. Effects of flow rate modifications on reported analgesia and quality of life in chronic pain patients treated with continuous intrathecal drug therapy. *Pain Med* 2011; 12: 571-6.

[5] Buchser E, Durrer A, Chédel D, Mustaki JP. Efficacy of intrathecal bupivacaine: how important is the flow rate? *Pain Med* 2004; 5: 248-252.

[6] Mironer YE, Haasis JC, Chapple I, Brown C, Satterthwaite JR. Efficacy and safety of intrathecal opioid/bupivacaine mixture in chronic nonmalignant pain: A double blind, randomized, crossover, multicenter study by the National Forum of Independent Pain Clinicians (NFIPC). *Neuromodulation* 2002; 5: 208-13.

[7] Bernards CM. Cerebrospinal fluid and spinal cord distribution of baclofen and bupivacaine during slow intrathecal infusion in pigs. *Anesthesiology* 2006; 105: 169-178.

[8] Duarte RV, Raphael JH, Southall JL, Baker C, Hanu-Cernat D. Intrathecal inflammatory masses: is the yearly opioid dose increase an early indicator? *Neuromodulation* 2010; 13: 109-13.

[9] Duarte RV, Raphael JH, Southall JL, Baker C, Ashford RL. Intrathecal granuloma formation as result of opioid delivery: systematic literature review of case reports and analysis against a control group. *Clin Neurol Neurosurg* 2012; 114: 577-84.

[10] Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andrés J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs MS, Kim P, Kumar K, Leong M, Liem L, McDowell GC 2nd, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt W, Yaksh T, Mekhail N. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation* 2012; 15: 436-64.

[11] Guy W. Clinical global impressions. In: ECDEU Assessment Manual for Psychopharmacology. Rockville: National Institute of Mental Health, 1976.

[12] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; 113: 9-19.

[13] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983; 17: 45-56.

[14] Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. *Ann Med* 2001; 33: 337-43.

[15] Senn S. Cross-over trials in clinical research. 2nd Ed. Chichester: Wiley, 1993. pp. 211-219.

[16] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; 41: 582-592.

[17] Schouten H, Kester A. A simple analysis of a simple crossover trial with a dichotomous outcome measure. *Stat Med* 2010; 29: 193-198.

[18] Rosenkranz GK. Analysis of cross-over studies with missing data. *Stat Methods Med Res* 2015; 24: 420-433.

[19] Reck T, Chang EC, Béchir M, Kallenbach U. Applying a part of the daily dose as boli may improve intrathecal opioid therapy in patients with chronic pain. *Neuromodulation* 2016 [Epub ahead of print]

[20] Flack SH, Anderson CM, Bernards C. Morphine distribution in the spinal cord after chronic infusion in pigs. *Anesth Analg* 2011; 112: 460-4.

[21] Flack SH, Bernards CM. Cerebrospinal fluid and spinal cord distribution of hyperbaric bupivacaine and baclofen during slow intrathecal infusion in pigs. *Anesthesiology* 2010; 112: 165-73.