A randomised controlled study of epidural fentanyl analgesia following lumbar laminectomy

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Background

Lumbar laminectomy is a surgical procedure commonly performed within neurosurgical, spinal and some orthopaedic departments. It is usually carried out for lumbar canal stenosis which is a degenerative condition mostly affecting those over 40 years of age.

To perform a laminectomy the erector spinae muscles have to be dissected from the spinous processes of the lumbar vertebrae. The posterior bony arch (lamina) is then removed. The combination of these two manoeuvres results in significant post-operative pain.

The standard post-operative analgesic regime involves local anaesthetic (Bupivicaine or Lidocaine) to the superficial tissues and oral analgesics. This is usually supplemented by intravenous or rectal analgesics. Opioid analgesics are used routinely. Constipation, delayed mobilisation and inadequate analgesia are seen frequently.

A new alternative analgesic approach has been developed. This involves passing an epidural catheter cranially and injecting 100micrograms of fentanyl into the epidural space approximately 10cms above the operative site. Following this single bolus injection the catheter is removed, the laminectomy wound closed and the patient is managed in the usual way.

This technique has been trialled successfully. The length of stay was reduced from 4.1 to 3.3 days when compared to a historical control group. 17 patients were given epidural fentanyl without any complications. A larger prospective randomised controlled study is therefore required to confirm these results.
Literature

Epidural anaesthesia is used occasionally in spinal surgery as an alternative to general anaesthesia\(^1\). The agents used usually include a local anaesthetic such as Bupivicaine with additives including opioid analgesics, clonidine, adrenaline or neostigmine.\(^1\) The catheter may be left in situ to provide post-operative analgesia.

Fentanyl selectively blocks the A\(\delta\) and c pain fibres when given intrathecally. It is highly lipid soluble with a short half life of 1-4 hours. When given epidurally it is not clear whether it works by crossing the dura and blocking pain fibres or by entering the blood and working at the supraspinal level.\(^2\)

The use of epidural local anaesthetic whilst effective may frequently result in lower limb weakness. This could mask the development of a post-operative haematoma and therefore epidural local anaesthetics should be avoided in spinal surgery.

The side effects of epidural fentanyl may include respiratory depression. There have been reported cases of delayed respiratory depression following intravenous use. However a recent Cochrane review suggests that there is no significant difference in the incidence of respiratory depression, nausea or vomiting with epidural versus systemic analgesia. Sedation is less common with epidural analgesia. Urinary retention (OR 3.5 95% CI 1.63 to 7.51; NNH 4.5; 95% CI 2.3 to 12.2), pruritis (OR 4.74 95% CI 1.76 to 12.78; NNH 6.8; 95% CI 4.4 to 15.8) and hypotension (OR 2.78 95% CI 1.15 to 6.72; NNH 6.7; 95% CI 3.5 to 103) are more common.\(^3\)

The previous study was performed in 2005 but has not been published. 17 patients were given epidural fentanyl. 11 of these were treated in the NHS and a control group of 7 NHS patients treated by the same surgeon was identified retrospectively. The length of stay was 4.1 days in the NHS control group, 3.3 days in the NHS treatment group and 2.3 days in the private treatment group. No complications were observed.
Null Hypothesis

Epidural fentanyl is not more effective at controlling post-operative pain than current standard analgesic techniques.

Method

Inclusion criteria

Patients will be eligible for this study if they are
- Having a lumbar laminectomy for degenerative canal stenosis
- 18 years or older
- Able to give informed consent for this trial

Patients will be excluded if
- There is a CSF leak or the dura is opened
- Contraindication to fentanyl as follows Respiratory depression, obstructive airways disease. Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation. Known intolerance to fentanyl
- Vulnerable group or unable to consent

Consent

Patients will be given the information sheet about the study when or soon after they are placed on the waiting list for surgery. Patients will undergo full formal informed consent in preadmission and at least 24 hours prior to surgery

A consent form and patient information leaflet have been developed (attached).

Randomisation

Randomisation will be between surgery with epidural fentanyl v surgery with routine post-operative analgesia. The “routine post-operative analgesia” will usually involve oral, rectal or iv opioids but is left to the discretion of the anaesthetist involved.

The patients will be blinded as to which arm of the trial they have been randomised to. The surgeon cannot be blinded. This is therefore a single blind trial.
Randomisation will be achieved using the opaque envelope technique. Stratification within centres will be applied.

**Procedure**

Following full informed consent the patient will be randomised to epidural fentanyl or the control group.

A standard laminectomy and lateral recess decompression will be performed.

In the epidural fentanyl group 100 micrograms of fentanyl will be mixed with 8mls of normal saline to make 10mls of 10micrograms/ml fentanyl. An epidural catheter is then passed cranially in the midline, outside the dura 10cms above the top of the laminectomy. The fentanyl can then be injected slowly over about 60 seconds. The epidural catheter is removed and the wound closed in the usual way.

Intraoperative analgesia may be given as per the anaesthetists and surgeons usual practice. Post-operative management will involve early mobilisation and analgesia as required. Patients will be kept in recovery for 1 hour. An alarmed pulse oximeter, ½ hourly observations and respiratory rate measurements will be carried out for a minimum of four hours.

**Outcome measures**

The primary outcome measure will be a visual analogue pain score. This will be recorded in recovery, on the first and second post-operative days.

Secondary outcome measures will be:
- length of post-operative hospital stay
- post-operative analgesia required – total dose and types per 24 hours for first two days. All opioid analgesics will be converted to morphine equivalents
- Side effects by day 2 including urinary retention, nausea, vomiting and pruritis.

**Statistical Plan**

Pain scores are ranked data that should be distributed in a normal distribution. Analysis will therefore be with a Mann Whitney rank sum test. Length of hospital stay is continuous data and will be analysed using a t test. The prevalence of side effects will be analysed using a Chi2 test. The total intra and post-operative analgesia requirement will be converted to morphine equivalents and analysed using a t test. No subgroup analysis will be undertaken.

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Power calculation

There is no available data to base a power calculation on.

However it is estimated that 35% of subjects v 65% of controls will have a pain score of more than 5. Therefore a sample size of 100 will be required to show benefit at p<0.05 with 80% power.

This study is therefore designed as a 100 patient pilot study

Safety Reporting Procedures

See appendix 1

Trial termination

The trial will end when the last patient is discharged from hospital.

References


2. Liu SS, McDonald SB Current issues in spinal anaesthesia Anaesthesiology, V94, No 5, May 2001

Appendix 1 : Safety Reporting Procedures

1.1 Definitions

1.1.1 Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

1.1.2 Adverse reaction of an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

1.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the summary of product characteristics (SmPC). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

1.1.4 Serious adverse event or serious adverse reaction

Any untoward medical occurrence or effect that:
- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients’ hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Epidural fentanyl following lumbar laminectomy version 2
EUDRACT 2006-001759-37


1.2 **Expected adverse drug reactions**

Adverse events reported in association with fentanyl use are listed below:

**Central & Peripheral Nervous System Disorders**
Common: Muscle rigidity (which may also involve the thoracic muscles), myoclonic movements, dizziness

**Cardiovascular Disorders, General**
Common: Hypotension

**Gastro-Intestinal System Disorders**
Very Common: Nausea, vomiting

**Psychiatric Disorders**
Very Rarely: Insomnia, sexual dysfunction (eg decreased libido)

**Body as a Whole – General Disorders**
Uncommon: Allergic reactions (such as pruritus, urticaria)

When a neuroleptic is used with fentanyl, the following adverse reactions may be observed: chills and/or shivering, restlessness, post-operative hallucinatory episodes and extrapyramidal symptoms.

1.3 **Expected Serious Adverse Events**

Adverse events reported in association with fentanyl use are listed below:

**Heart Rate and Rhythm Disorders**
Common: Bradycardia
Rarely: Asystole

**Respiratory System Disorders**
Common: Apnea, respiratory depression
Uncommon: Laryngospasm
Rarely: Secondary rebound respiratory depression

**Body as a Whole – General Disorders**
Uncommon: Allergic reactions (such as anaphylaxis, bronchospasm)

1.4 **Recording and evaluation of adverse events**

Individual adverse events will be evaluated by the investigator and, where indicated, they will be reported to the sponsor for evaluation. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

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EUDRACT 2006-001759-37
The sponsor will keep detailed records of all AEs reported to him by the investigators and to perform an evaluation with respect to seriousness, causality and expectedness.

1.4.1 **Assessment of seriousness**

**Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated

**Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

**Severe:** Significant impairment of functioning; the subject is unable to carry out usual activities and/or the subject’s life is at risk from the event.

1.4.2 **Assessment of causality**

**Probable:** A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

**Possible:** A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

**Unlikely:** A causal relation is improbable and another documented cause of the AE is most plausible.

**Unrelated:** A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

1.5 **Reporting adverse events**

The sponsor is responsible for the prompt notification to all concerned investigators, the Research Ethics Committee and competent authority of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority’s authorisation to continue the trial in accordance with Directive 2001/20/EC.

1.6 **Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)**

All suspected adverse reactions related to fentanyl which occur in the trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

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EUDRACT 2006-001759-37
1.6.1 Who should report and whom to report to?

The sponsor will report all the relevant safety information previously described to the MHRA and to the Ethics Committee concerned. The sponsor will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

1.6.2 When to report?

1.6.2.1 Fatal or life-threatening SUSARs

The MHRA and the Research Ethics Committee will be notified as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information will be sought and a report completed as soon as possible. It will be communicated to the MHRA and the Ethics Committee within an additional eight calendar days.

1.6.2.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues will be reported to the MHRA and the Ethics Committee as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information will be given as soon as possible.

1.6.3 How to report?

1.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports will be submitted within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product,

b) an identifiable subject (e.g. study subject code number),

c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,

d) an identifiable reporting source,

and:

- a unique clinical trial identification (EudraCT number)
- a unique case identification.
1.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality will be actively sought from the reporter or other available sources. The sponsor will report further relevant information after receipt as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

1.6.3.3 Format of the SUSARs reports

Electronic reporting will be used for expedited reporting of SUSARs to the MHRA. The format and content as defined by the Guidance 1 will be adhered to.