RANDOMISED DOUBLE-BLIND COMPARISON OF MORPHINE VS A MORPHINE-ALFENTANIL COMBINATION FOR PATIENT-CONTROLLED ANALGESIA

by

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ABSTRAK

Kaedah penggunaan analgesi/ubat penahan sakit kawalan pesakit (AKP) telah dilaksanakan semenjak 30 tahun dahulu lagi sebagai satu kaedah alternatif untuk mengawal selia penggunaan analgesi/ubat penahan sakit selepas pembedahan.

Ianya membolehkan pesakit mengawal sendiri sejumlah kecil opiod yang diperlukan dengan lebih baik dan berkesan.

Jumlah ubat yang diberikan kepada pesakit telah dihadkan berdasarkan beberapa faktor antaranya; jumlah permintaan terhadap dos, had masa kekunci dan jeda masa kekunci misalnya setiap jam atau setiap 4 jam .

Kajian ini dijalankan secara rawak untuk mengkaji kesan penggunaan diantara campuran morfin dan alfentanil dengan hanya penggunaan morfin, keatas pesakit yang menjalani pembedahan 'Caesarean'.

Selepas pembedahan, pesakit-pesakit yang telah dipilih secara rawak dan diberi analgesi/ubat penahan sakit iaitu campuran 0.75 mg morfin dan 0.125 mg alfentanil (Kumpulan MA dimana jumlah pesakit adalah seramai 40 orang) atau 1.5 mg morfin (Kumpulan M juga dengan jumlah bilangan pesakit seramai 40) dengan had masa kekunci 8 minit dan tanpa had dos- masa atau infusi dasar.

Pemerhatian secara klinikal dibuat pada 24 jam pertama dan pesakit dikehendaki menjawab soalan soal –selidik yang telah disediakan.

Terdapat perbezaan yang ketara bagi penggunaan analgesi/ubat penahan sakit kawalan pesakit(AKP) oleh kedua-dua kumpulan dengan purata AKP yang diterima oleh Kumpulan MA adalah lebih besar (41.0) berbanding dengan Kumpulan M (27.4) tetapi skala visual analog bagi sakit yang diukur pada 2 jam, 4 jam, 6 jam dan 24 jam di dapati tiada perbezaan langsung. Insiden kesan sampingan dari penggunaan kedua-dua ubat

tersebut adalah rendah. Tiada perbezaan ketara wujud di dalam jawapan yang diberikan oleh pesakit dalam borang soal selidik yang menilai kecepatan, keberkesanan dan jangkamasa analgesi dan secara keseluruhan kesemua pesakit sangat berpuas hati.

Penambahan alfentanil kepada morfin tidak memberi faedah untuk penggunaan analgesi/ubat penahan sakit kawalan pesakit.

ABSTRACT

Patient-controlled analgesia (PCA) has been used for the past 30 years as an alternative method to administer postoperative analgesia. Patient-Controlled Analgesia allows patients to self-administer small boluses of opioids, providing better dose titration and regulation. The quantity of analgesic available to the patient is limited by the prescribed patient-controlled analgesia variables; demand dose size, lockout period and hourly or 4-hourly limits.

In a randomized, double-blind study, I compared a combination of morphine and alfentanil with morphine alone for patient-controlled analgesia after Caesarean section under spinal anesthesia. After surgery, patients were randomly allocated to receive patient-controlled analgesia with a bolus dose of either morphine 0.75 mg plus alfentanil 0.125 mg (Group MA, n= 40) or morphine 1.5 mg alone (Group M, n=40) with a lockout interval of 8 minute and no hourly dose limit or basal infusion. Clinical assessments were made in the first 24 hours, after which patients completed a written questionnaire. There was a significance difference between groups in patient-controlled analgesia usage with the mean of patient-controlled analgesia boluses received by group MA bigger (41.0) as compared to group M (27.4) but the visual analogue scale scores of pain measured at 2, 4, 6 and 24h were not significant.

There was a low incidence of side-effects in both groups. In the questionnaires, there were no differences in grading for speed of onset, effectiveness of analgesia, duration of analgesia and overall patient satisfaction. Addition of alfentanil to morphine does not have any advantages for patient-controlled analgesia.

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1. INTRODUCTION

Despite constantly increasing understanding of pain mechanisms and improved technology in pain therapy for the anaesthetist, the provision of adequate postoperative pain relief is still a challenge. Unfortunately, postoperative pain relief, which is conventionally provided by parenteral medication, is often incomplete (*Keeri-Szanto and Heaman 1972; Tammisto 1978; Tammisto and Tigerstedt 1982; Ready 1999).* As far as we know, conventional prescription of opioids—to be given by nurses 'as required'—seldom produces an adequate level of analgesia. In addition, it is impossible to accurately predict what analgesic dosage will be required to provide sufficient pain relief or how much pain a patient will experience after an operation. Adequate pain control may even improve recovery from surgery by reducing stress and improving pulmonary function *(Craig 1981; Bonica 1987; Kehlet 1989, 1994; Scott and Kehlet 1988).* Optimal postoperative analgesia may also reduce postoperative complications and shorten postoperative recovery (*Kehlet 1994; de Leon-Casasola et al. 1994).* Patient-Controlled Analgesia (PCA) has become an established technique for the treatment of postoperative pain *(Sechzer 1968; Scott 1970; Keeri-Szanto 1971; Tammisto 1978; Ready 1990; Zimmermann and Stewart 1993; Lehmann 1995).* It has been shown to offer a number of advantages, including good analgesia, avoidance of fluctuations in analgesia, lower total analgesic dosage, and improved patient satisfaction. This method allows self-administration of small, frequent doses of analgesics to maintain a state of constant pain control. The effectiveness and safety of patient controlled-analgesia with a number of opioids have already been demonstrated *(Lehmann 1995; Ready 2000)*; however, the optimal opioid has not yet been found. The most popular opioid in patient controlled-analgesia has been morphine *(White 1988;*

Stanley et al. 1996), but also most other opioids have been tested *(Lehmann 1995*). Ideally, the analgesic for patient controlled-analgesia should have a rapid onset of analgesic action, be highly efficacious in relieving pain, have an intermediate duration of action (30-60 minutes), produce no tolerance or dependence, and have no or minimal side-effects or adverse drug interactions *(White 1988; Etches 1999*).

The potency of a drug is affected by its ability to gain access to receptors as well as the ease with which it binds. The physico-chemical properties of opioids have important effects on their activity. The ability of a drug to diffuse through membranes to reach receptors depends upon its lipid solubility and the relative concentrations of its ionized and non-ionized forms. These properties can predict the actions of different opioids.

Many different opioids have been used for patient-controlled analgesia (PCA) but no single drug has been found to be consistently better than morphine. However, morphine has the disadvantage of being a hydrophilic molecule (octanol/pH 7.4 buffer partition coefficient 1.4) and low un-ionized fraction (24 %); that enters the central nervous system slowly; thus morphine has a slow onset of action. In comparison, alfentanil has a much faster onset because of its greater lipid solubility (octanol/pH 7.4 buffer partition coefficient 129) and high un-ionized fraction (89%) in plasma at physiological pH. Alfentanil is therefore more freely diffusible with a faster onset and shorter duration of action. Thus, the typical side-effects of opioids, such as nausea and vomiting, sedation, respiratory depression, and pruritus which may sometimes hamper the successful application of patient controlled-analgesia will be lessened *(Nottcutt and Morgan 1990; Lehmann 1993; Baxter 1994*).

2. OBJECTIVES

General:

This study is design to test the hypothesis that the combination of morphine with the faster-acting opioid, alfentanil, would improve analgesia compared with morphine alone when used for patient controlled-analgesia.

Specific:

1) To compare the potency, efficacy and side-effects of the two opioids in combinations (morphine and alfentanil) and morphine alone.
2) To evaluate the safety of and patient satisfaction with intravenous patient-controlled analgesia.

3. METHODOLOGY

After obtaining approval from the University Clinical Research Ethics Committee, I recruited, randomized and double-blinded 80 ASA physical status I and II women undergoing Caesarean section. The study was conducted at Hospital University Sains Malaysia and Hospital Kota Bharu from September 1999 till October 2000. Sample size was based on data from a previous study of patient controlled-analgesia after Caesarean section, from which I calculated that 38 patients per group would be required to ensure 80% power to detect a difference of 15 mm on a 100-mm visual analogue scale (VAS) for pain on movement, with a type 1 error probability of 0.05. All patients gave informed consent and were instructed on the use of the VAS and a patient controlled-analgesia device (Graseby 3300patient controlled-analgesia Pump, Graseby Medical Limited). Patients were kept nil by mouth from 12 midnight or at least 6 hours prior to surgery, received 150 mg ranitidine orally the night before and the morning of surgery and 0.3 M sodium citrate 30 ml just before transferred to the operating theatre.

After intravenous preload of 1000 ml lactated Ringer's solution and skin cleaned with antiseptic solution and skin infiltration with lignocaine 2%, a 25-G Quincke spinal needle was inserted at the Lumbar 2-3 or Lumbar 3- 4 vertebral interspace with the patient in the lateral position. Spinal anaesthesia was established using 2.2 ml hyperbaric bupicaine 0.5%. Intravenous ephedrine was given as required for hypotension. Nitrous oxide or small intravenous doses of fentanyl were given as required for intra-operative analgesia, at the anaesthetist's discretion.

After surgery, patients were randomly allocated, by drawing of shuffled, coded envelopes, to receive post-operative analgesia by patient controlled-analgesia using one of two solutions: morphine 0.5 $mg \cdot ml^{-1}$ plus alfentanil 0.083 $mg \cdot ml^{-1}$ (group MA, n =

40) or morphine 1mg·ml^{-1} alone (group M, n = 40). The ratio of alfentanil to morphine (1:6) was based on published data on equipotency ratios for opioids used for patient controlled-analgesia calculated according to pain scores and drug consumption. The patient controlled-analgesia solutions were prepared by a staff nurse who was instructed and supervised on how to prepare the solutions. The patient controlled-analgesia device was connected to a dedicated intravenous catheter and set to deliver a bolus dose of 1.5 ml; thus at each successful patient controlled-analgesia demand, patients in group MA received morphine 0.75 mg and alfentanil 0.125 mg, and patients in group M received morphine 1.5 mg. A lockout time of 8 minute was used with no dose limit over time, in keeping with our standard protocol. Patients were observed by the nursing staff in the postnatal ward according to the usual protocol for patient controlled-analgesia *i.e.* the hospital APS (Acute Pain Service) protocol, which includes hourly recording of level of consciousness and respiratory rate. Metoclopramide 10 mg intramuscularly was charted as required to treat nausea and vomiting. The on-call anesthetic Medical Officer was available to attend at all times.

A staff nurse, who was blinded to the patient's group, assessed each patient at 2, 4, 6 and 24 hour after surgery. At each assessment, patients were asked to grade their pain at rest, pain on coughing, nausea, dizziness and sleepiness using the visual analogue scale. At 24 hours, the total numbers of patient controlled-analgesia demands and boluses delivered were obtained from the electronic memory of the patient controlled-analgesia device. In addition, patients were given a written questionnaire to complete which asked their assessment of aspects of the analgesia obtained from the patient controlled-analgesia regimen (Appendix). Assessments were made on an 11-point numerical scale.

Chi-squared tests and Student T- tests were used as appropriate to compare categorical data and numerical data respectively, between 2 groups. Repeated Measure Analysis of Variance (ANOVA) was applied to compare mean scores of visual analogue scale and Prince Henry scores for pain, and visual analogue scale of side-effects between 2 groups. Other demographic variables effects were tested if they should be included in the model. The significant level was set at 0.05 and 95% confidence intervals were applied as appropriate.

4. LITERATURE REVIEW

4.1 PATIENT-CONTROLLED ANALGESIA (PCA)

4.1.1 Principles and development of patient controlled-analgesia

Traditional techniques for the provision of postoperative analgesia by intermittent intravenous or intramuscular injections of an opioid drug do not meet the needs of every patient. Patient-Controlled Analgesia (PCA) allows every patient to self-administer small boluses of opioids, providing better dose titration and regulation (*Bennett et al. 1982*). This avoids the 'peak and valley' effects encountered with conventional intramuscular administration of analgesics. Stable drug plasma concentration is an important goal of postoperative pain management. When using patient controlled-analgesia, the plasma concentration at which the patient becomes sufficiently uncomfortable to make a dose demand has become known as the minimum effective (analgesic) concentration (ME(A)C) (*Dahlstrom et al. 1982; Gourlay et al. 1988; Lehmann 1995; Woodhouse and Mather 2000*). Intrapatient variation in MEAC for morphine in the treatment of postoperative pain has been relatively small (*Dahlstrom et al. 1982*), but interindividual variation in the plasma concentration of opioid required to achieve adequate pain relief has been large (*Dahlstrom et al. 1982; Gourlay et al. 1988*). As a result, self-administration of opioids after abdominal and orthopaedic surgery has been characterized by considerable variability in individual morphine consumption (*Lehmann et al. 1985*).

Patient controlled-analgesia allows patient to take direct control of administration of discrete doses of an analgesic agent for the relief of pain. In practice the patient is instructed to press a push-button whenever pain relief is required. If preset

time and/or dose limits are not exceeded, then activating the demand mechanism results in a dose of drug being administered; this may be systemically or spinally. In this way, patient controlled-analgesia is a simple feedback loop that does not require the intervention of medical or nursing staff at the time of each analgesic demand. Patient controlled-analgesia can provide better pain relief than intermittent intramuscular injections or continuous infusions of opioids, but not automatically; patient controlled-analgesia must be understood by medical and nursing staff and the patient to reach its full potential.

An important advantage of patient controlled-analgesia is its ability to minimize the time-delay between perception of pain and administration of medication (*Lutz and Lamer 1990*).

The first attempts to establish intravenous patient controlled-analgesia were made in the late 1960s, after patient controlled-analgesia with intermittent intravenous doses of narcotic analgesics was first described by Philip Sechzer (*Sechzer 1968, 1971, 1990*), who reported that such a patient-controlled analgesic-demand for the alleviation of pain and for the reliable measurement of pain and pain relief had been under study since 1965. In this system, patients when they felt pain during recovery from surgery were instructed to press a button. When this button was pressed, a nurse observer administered 1 ml of pethidine- or morphine-containing solution (*Sechzer 1968, 1971*). At the same time, the concept of patient controlled-analgesia was developed independently in the U.K. by Scott, who permitted the patients to operate a hinge-lever spring clamp that restrained the intravenous drip flow of pethidine, so patients controlled their own intravenous infusion rate of analgesic *(Scott 1970)*. In 1970, Forrest and his co-workers described a more sophisticated apparatus (Demand Dropmaster), which after the patient pressed the button on a handgrip device,

automatically dispensed intravenous analgesic drugs on demand (*Forrest et al. 1970*). Keeri-Szanto eventually developed a commercial machine with an electrically controlled syringe pump (*Keeri-Szanto1971*). The analgesic efficacy of patient controlled-analgesia has been demonstrated to be superior to that obtained with intermittent intramuscular injections (*Keeri-Szanto and Heaman 1972*). After this, several experimental systems for the self-administration of analgesics have been described (*Evans et al. 1976; Tammisto 1978; Hull et al. 1979; Hull and Sibbald 1981; Rosenberg et al. 1984*). With the development of microprocessors improving the technology of patient controlled-analgesia pumps, the clinical use of patient controlled-analgesia became more popular and widespread (*Kay 1981; Rowbotham 1992*).

Patient controlled-analgesia is an effective and safe means to provide pain relief for cancer patients (*Citron et al. 1986*), and the technique has been proven beneficial in patients ranging in age from children as young as 5 years to frail, elderly men (*Egbert et al. 1990; Irwin et al. 1992*).

In patients undergoing bone marrow transplantation and in women after abdominal hysterectomy, patient controlled-analgesia therapy decreases the morphine requirement compared to that in a continuous morphine infusion (*Hill et al. 1990; Parker et al. 1991*).

The continuous background infusion of morphine during patient controlled-analgesia analgesia has been studied extensively, and shown to increase morphine consumption, sedation, and respiratory depression without improving pain relief or patient satisfaction (*Owen et al. 1989; Wu and Purcell 1990; Parker et al. 1991; 1992; Tigerstedt et al 1991; Russell et al. 1993; Baxter 1994; Etches 1994*). On the other hand, following abdominal surgery, a continuous morphine infusion of 1 mg/h with intravenous patient controlled-analgesia (morphine 1 mg bolus and 5 min lockout

period) has improved analgesia during the first 24 hours. This method was associated with a greater incidence of complications than with intravenous patient controlled-analgesia alone (*Dawson et al. 1995*). In the light of all this, the efficacy of combining a continuous infusion with intravenous patient controlled-analgesia is uncertain.

Patient-controlled analgesic administration offers the best individualization, and in addition, patient controlled-analgesia should be considered for those patients with the most resistant pain (*Tammisto 1978; Tammisto and Tigerstedt 1982*).

4.2 PATIENT-CONTROLLED ANALGESIA: CAN IT BE MADE SAFER?

Over the past thirty-five years, Patient-Controlled Analgesia (PCA) has developed from a research tool to become a major component in the treatment of pain. Originally the scope of patient controlled-analgesia was limited to intravenous therapy for postoperative analgesia in adults, but with its proven efficacy, its range of applications has grown. Patient controlled-analgesia is now used in paediatric surgery, obstetrics, trauma, burn's patients, those receiving immunotherapy and in a variety of medical conditions such as acute myocardial infarction, sickle-cell crisis and herpes zoster. In addition, in some areas, the intravenous route of administration has been replaced by oral, sublingual, subcutaneous, intramuscular and epidural patient controlled-analgesia.

Most physicians and patients would still agree with Rosen's statement that '*.....it is better to be in pain than killed by analgesic*'. However, recent audits of current practice with patient controlled-analgesia both in the United States and England indicate that effective postoperative analgesia can usually be combined with its safe administration. A survey from the Cleveland Clinic Foundation reviewed medication

mishaps in 3,299 patients who were receiving patient controlled-analgesia. There were 42 mishaps (1.2%): 22 were operator related, 15 equipment malfunctions and five cases of adverse drug reaction (norpethidine toxicity in four cases and morphine overdose compounded by renal failure in the remaining patient). A comprehensive survey of the first thousands patients involved with patient controlled-analgesia in a district general hospital in the U.K. showed that technical problems (e.g. deprogramming and disorders of trigger mechanism) were more common than adverse clinical effects. Respiratory problems occurred in 2.5% of all patients on patient controlled-analgesia, but in less than half of these patients was it necessary to stop the patient controlled-analgesia treatment prematurely. Two factors may be responsible for the apparently low complication rate. First, patient controlled-analgesia machines are not available in the majority of hospitals: insufficient numbers of machines to cover all postoperative patients dictate that these are used on a preselected group who may be in general fitter, younger and undergoing more major surgery. Second, it is still the case that patient controlled-analgesia is being popularized by a relatively small group of enthusiastic anaesthetist who spend considerable time pre- and postoperatively in the management of these patients.

There are groups of patients in whom patient controlled-analgesia may be unsuitable, or potentially dangerous and difficult to administer. Careful preoperative assessment will help to exclude these cases. Awareness of the aims and limitations of the treatment, for both nursing and medical staff, becomes better developed following comprehensive education. Similarly, patients undertaking patient controlled-analgesia therapy need teaching in the technique along with information regarding potential worries they may have about the therapy. Dramatic technological advances with patient controlled-analgesia equipment over the past five years have dictated the equipment

familiarization is essential for all involved in its delivery. If patient controlled-analgesia is to be used safely in any hospital, its introduction must have minimal impact on current nursing and medical routine. Moreover, potential problems and interactions between the different components of the patient controlled-analgesia system are becoming evident. Finally, clinical audit is essential to allow critical appraisal of the efficacy of this treatment modality along with potential adverse effects.

4.3 PATIENT SELECTION

For the technique to be effective, patients must be able to understand the mechanism of their analgesia. A painful stimulus must be assessed by the patient who can subsequently elicit an appropriate response, i.e. a push of the patient controlled-analgesia button. This may not be possible in the very young, who are unable to make the connection between pain and relief; the very old, whose short term memory may preclude the retention of even the simplest of instructions; and in those patients with acute confusional states or organic brain syndromes.

Although most patients cope well with patient controlled-analgesia, there are some in whom the concept of complete control may be intimidating and where patient controlled-analgesia is totally unsuitable. The success, therefore, of this therapy can be significantly limited by the psychological make-up of the patient. The concept of 'locus of control' was described in the mid-sixties by Rotter and subsequently developed into a Multidimensional Health Locus of Control (MHLC) scale that categorized patients depending on their attitudes to behaviour and subsequent reinforcement. Those who see their own actions as contributing to the reinforcement have an 'internal' locus of control and tend to be active in controlling their environment. These patients respond well to

patient controlled-analgesia and are able to use it effectively. Conversely, patients who have an 'external' locus of control relate positive reinforcement to other people or events, resulting in loss of control, strong reliance on others and failure of the technique. Neuroticism, anxiety state and anxiety trait are positively correlated with postoperative pain scores. Whether preoperative questionnaires are a practical screening procedure for institution of patient controlled-analgesia is under debate. Until a uniform, reproducible and a simple assessment is available, clinical impression and evaluation by the physician and nurse will be the most important aspect in patient selection.

Patients who are intravenous drug abusers present a particularly difficult problem both in assessment of analgesic requirements and therapeutic effect. The analgesic end-point sought by non-addicted patients is tempered by their desire to stay as alert as possible. Keeri-Szanto contrasted these to addicted patients who '... *administered narcotics to the brink of unconsciousness, "coming up for air" only long enough to trigger the administration of more drugs*'. Some centers allow intravenous (e.g. heroin), and inhalational (e.g. cocaine and 'crack') drug abusers, free access to their patient controlled-analgesia service. Patients suspected of seeking 'high' rather than analgesia, or tampering with the patient controlled-analgesia devices, have these withdrawn. Reliance is placed on the honesty of these patients, to comply with treatment. We have found patient controlled-analgesia less than ideal with these patients, due to their continuous drug-seeking behaviour, interference with patient controlled-analgesia devices and manipulative personalities. Reliable feedback concerning the efficacy of the treatment cannot be differentiated from a desire to obtain a 'high'. The increased nursing and medical time that is involved with using patient controlled-analgesia in these patients must be considered, especially when it may interfere with the treatment of other patients and result in damage to equipment.

The consideration of patients for patient controlled-analgesia who are or who may become hypovolemic presents another difficult therapeutic dilemma. Analgesics agents are ideally administered to these patients in small intravenous boluses, yet constant assessment of neurological and cardiovascular parameters is essential, due to preferential distribution of blood flow to the heart and brain in such shocked individuals (Figure 4.1). Whilst the problems of erratic absorption and potential bolus administration following reperfusion are recognized with intramuscular injection, opinion is divided as to whether patient controlled-analgesia is safe in this group of patients. In a recent study of ours in which different sized bolus doses for patient controlled-analgesia were compared, two patients developed respiratory depression requiring naloxone administration. Both of these patients had hypovolemia secondary to covert blood loss. These support recommendations made by Tamsen and colleagues that patient who have labile cardiovascular parameters are unsuitable for patient controlled-analgesia and contrasts with the experience of Notcutt who advocate the usefulness of patient controlled-analgesia in this group of patients. Caution is advised if patient controlled-analgesia is used in any patient with an unstable cardiovascular system. Careful pre- and postoperative assessment by anaesthetic and nursing staff will help to identify all these patient subgroups and assess their suitability for patient controlled-analgesia accordingly.

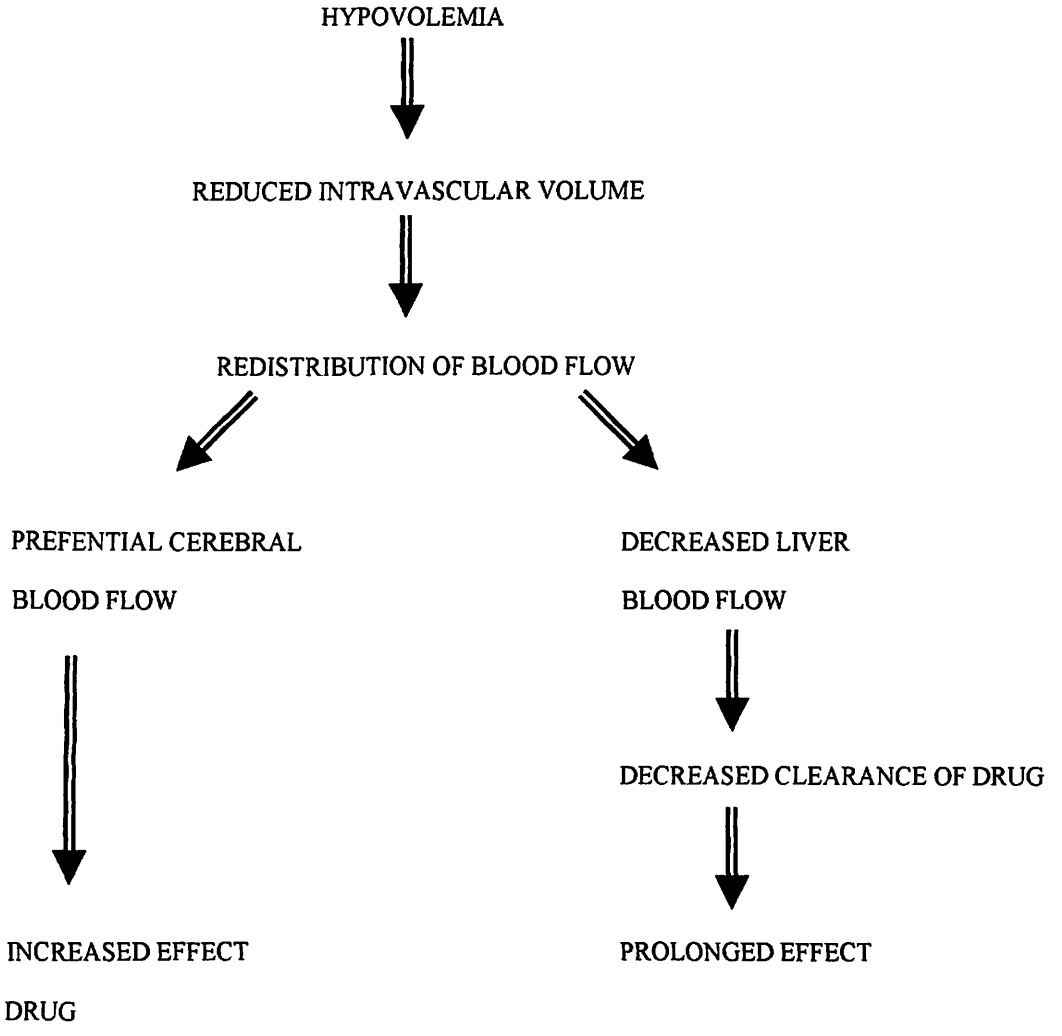

Figure 4.1. - The effects of delivery of patient controlled-analgesia bolus in hypovolaemic patients.

4.4 EDUCATION

Comprehensive education of patients, relatives, nursing and medical staff, both anaesthetic and surgical, can be the most important measure to ensure safety and efficacy of patient controlled-analgesia. Patients can be educated by the anaesthetist at the preanaesthetic clinic and/or preoperative visit, and this should be reinforced by ward and theatre staff. Patients' expectations and apprehensions need to be identified preoperatively before patient controlled-analgesia is instituted. A recent survey revealed

that the main disadvantage of patient controlled-analgesia as perceived by patients preoperatively was a reduction in the total time spent in contact with nursing staff. A smaller number worried about equipment failure, overdosage and addiction potential, whilst interestingly, very few saw patient controlled-analgesia as a way of totally relieving pain. *The control of pain seemed as important as the amount of pain reduction experienced.*

Other workers have indicated that careful and time consuming preoperative education for patients intending to use patient controlled-analgesia does not influence their ability to adequately self-administer analgesia. Although this can be reassuring for those patients who have missed preoperative education it does not indicate it is of little value. There are often worries and apprehensions that will only become apparent when instructing patients on the use of patient controlled-analgesia. The goals and safety features of patient controlled-analgesia also need explanation to relatives. In some circumstances, e.g. parent-controlled analgesia, relatives are given formal training and are encouraged to assist their children in activating the patient controlled-analgesia device. However, this breaks the negative feedback loop, whereby excessive sedation prevents the administration of further amounts of opioid. It can also be broken by concerned partners who activate the pumps for the patient. Obviously the consequences can be disastrous. Manufacturer of patient controlled-analgesia devices are now producing patient information sheets that attempt to explain and to answer in an attractive and simple way the use of patient controlled-analgesia and worries that the patients may have, and these also emphasize positive features of this treatment option. The value of this has not been studied. Work in other areas has shown that simply handing the patient such information is not enough, and that reinforcement by nursing

and medical staff is essential for information to be adequately and efficiently understood.

Education of nursing staff is ideally carried out by a dedicated nurse educator, whose aims are to teach the basic principles of patient controlled-analgesia, potential adverse effects, evaluation of problems and intervention strategies. This need to be addressed in all areas where patient controlled-analgesia is being used operation theatre, recovery and especially ward staff need to be fully acquainted with the theoretical and practical components of the technique, the equipment and the monitoring. Staffing changes along with quality assurance programs dictate that this cannot be accomplished in one visit so that ongoing education is essential to ensure continuity of care and prevention of mishaps.

Medical staffs, both anaesthetic and surgical, need to be fully aware of treatment options, equipment and its limitations, along with potential problems before prescribing patient controlled-analgesia. Historically the prescription and assessment of postoperative analgesia was under the control of the surgical team. The role of the anaesthetist in the postoperative period has grown in recent years in some hospital to include fluid balance, parenteral nutrition and now more than ever the prescription and delivery of analgesia. Surgeons may view this as interference if adequate information and communication is not presented by the anaesthetic staff. The inception of acute pain services has helped in providing a coordinated team approach, so that problems relating to patient controlled-analgesia can be collected centrally and a rapid and effective resolution facilitated.

Anaesthetist who prescribes patient controlled-analgesia need to be aware of the variants and variables involved in its administration. Variants include bolus demand, infusion demand, bolus demand plus constant infusion, and bolus demand with variable

infusion. The variables involved are the drug itself, dose size, maximum dose and lockout interval. Although most variants are available with all patient controlled-analgesia machines, the variable infusion rate was only present on one device. When considering variants and variables of patient controlled-analgesia, results of studies should not be extrapolated beyond the context of their design. Several studies have concluded that the addition of a background infusion of morphine to patient controlled-analgesia fails to improve analgesic effect, despite the administration of a larger dose of opioid and may increase side-effects such as sedation and confusion, while other workers support the benefits of a background infusion to increase analgesic efficacy. In another study, patients tended to seek analgesia, reflected as number of boluses, at the same rate, irrespective of the bolus dose size, suggesting that the actual bolus size prescribed is not as critical as previously thought. These studies only reflect experience with morphine, and further work with other opioids is needed. *Safe prescribing of patient controlled-analgesia depends on a thorough knowledge of the current patient controlled-analgesia literature along with sound clinical experience.*

4.5 EQUIPMENT

Malfunction of equipment was one of the biggest worries of the pioneers of patient controlled-analgesia, yet the paucity of articles regarding mishaps would suggest that such problems are not common. Equipment used for the administration of patient controlled-analgesia can be considered to fall into major components, the pump itself, and the accessories (e.g. the drug reservoir, delivery tubing, anti reflux valves and patient push-buttons).

Ideal characteristics of patient controlled-analgesia pumps were suggested by Norman at the first International Workshop on Patient-controlled Analgesia. Experience with a variety of pumps over the past six years had led us to propose the optimal characteristics of a patient controlled-analgesia pump. These should be borne in mind when considering purchase of these pumps.

4.5.1 Dual power supply

If mains operated, a reliable and long-acting battery back-up is required, with memory of previous program retained. Battery-only devices have the major advantage of portability and minimal hindrance to patients who may be ambulant. However, the battery life must be sufficiently long duration to allow uninterrupted use for individual patients, along with accurate rates of delivery at variable voltage inputs.

4.5.2 Drug specific pumps

These are designed for the individual agents, which negate the need to calculate concentrations and rates for individual drugs. Manufacturers' modifications of existing pumps, such as with plastic overlays that clearly identify the drug in the syringe along with the route of administration and communicate this information to the pumps' microprocessors, can be made. This may also help prevent the potential problem of attaching an intravenous line to an epidural or administering a drug destined for a vein into the epidural space. This has occurred with cephazolin, thiopentone, diazepam, potassium chloride and total parenteral nutrition with variable neurological sequelae.

4.5.3 Programming

The program should be simple to run, with no more than two steps needed to initiate any particular variable change. Menus should be easily read, illuminated for the night-time use, along with clearly labeled prompts on the screen. Once programmed, the machine should scroll the completed patient controlled-analgesia prescription for review before starting the infusion. Limits need to be set for maximum drug concentration, infusion rate, bolus rate and lockout interval. Alternatively, these can be inbuilt, and will be specific for each particular drug. Software protection against current surges and static interference is essential, not only to provide protection for the pump but also to prevent reprogramming and inactivation of alarms. The Graseby patient controlled-analgesia recently underwent a voluntary recall following the unprogrammed infusion of drug into a patient resulting from an electrostatic disturbance (ESD) associated with reconnection of power cord. Software modifications along with protection against electrostatic disturbance (ESD) may help prevent such problems in the future. One patient controlled-analgesia pump under development (by Bard) will have interchangeable preprogrammed 'chips' inserted into the pumps, so not only can the pump be dedicated to a particular drug, but a customized prescription for different modes of delivery and patient requirements can be used, thus removing yet another potential source of error, the setting-up of the patient controlled-analgesia prescription.

4.5.4 Activation buttons

The patient-machine interface needs consideration so that a continued pressure does not lead to persistent drug delivery and overdose. Ideally, activation of the pump should be initiated by a double button push or release of a cover on the activation button to prevent the accidental initiation of a bolus. By acting as a reaction-time tester, it may reduce the chance of a confused or sedated patient inappropriately demanding another dose. Fears that patients may not be able to carry out this more complicated activation process have not been confirmed in clinical practice.

4.5.5 Alarms

These should be of two types, relating to the significance of the problem and should combined audible and visible components; e.g. a quite, low-pitched alarm to warn against low battery, and a louder high-pitched alarm to warn air in line, line occlusion or empty syringe is advantageous. The patient should not be able to interfere with or silence these alarms.

4.5.6 Physical characteristics

Pumps need to be lightweight, robust and able to tolerate minor trauma, while their action should be silent to minimize disturbance to patients and those around them. Accuracy of the pump should be within 10% of set values. The high internal resistance of patient controlled-analgesia pumps combined with the use of high-volume syringes necessitates these devices generating high driving pressures. It is important that in

combination with epidural catheters and filters, the delivery characteristics is not altered and that occlusion alarms are not continually activated by the high line pressures that are generated.

4.5.7 Security

To avoid 'tampering' by untrained staff or patients it is mandatory that the analgesic reservoir cannot be detached from the pump during use. As most solutions are dilute, and due to the increasing use of epidural opioids, drug volumes required for patient controlled-analgesia devices are often large. This requires the frequent changing of syringes. As most medication mishaps are due to errors in making up solutions and initiating treatment, a large reservoir would be beneficial in reducing changeovers. This is present in the Abbott Pancretec Provider 5500 patient controlled-analgesia, Bard Ambulatory pump and Pharmacia 5800 patient controlled-analgesia device, which can house reservoirs containing hundreds of millimeters in a portable sealed case.

Some pumps (e.g. models in the Abbott Lifecare series and a version of the MDS 110 patient controlled-analgesia) have used dedicated prefilled syringes that can be replaced as necessary. Thomas and Owen reported a case of respiratory depression caused by a crack in a glass syringe leading to siphoning of a significant dose of morphine into a patient. Two factors combined to produce this complication; the presence of the crack allowed air to gain entry into the system whilst the adhesive label held the broken cartridge together thus simultaneously preventing the loss of drug. The siphoning effect was compounded, the pump being placed at a higher level than the patient.

Intravenous patient controlled-analgesia is commonly administered into the same cannula as the maintenance fluid. The importance of using anti-reflux valves in this situation has been reviewed in detail elsewhere. They are of value in preventing the retrograde flow of analgesic in the parallel line following an occlusion. Once the obstruction is released, a potentially dangerous bolus may be suddenly presented to the patient. The characteristics of the ideal anti-reflux valve are shown in Table 4.1.

Table 4.1-Characteristics of the 'ideal' anti-reflux valve

1. Low stored volume.
2. No retardation of fluid flow.
3. Incorrect orientation impossible.
4. Integral part of administration set.
5. Cheap.

Large bore tubing is needed to prevent retardation of fluid flow if resuscitation is required. Valves and tubing of low compliance prevent the occurrence of a large stored volume of analgesic that may occur if a pump continues to work against an obstruction. This may be subsequently delivered as a bolus to the patient. Thus careful matching of pumps to delivery systems and drug dilutions is of great importance. The potential bolus delivery from one pump and delivery system following release of an occlusion could be up to the equivalent of 6mg of morphine, whilst from another pump using the same system the bolus may only approximate to 2 mg. The compliance of the system affects not only the stored volume characteristics but also detection of occlusion alarms.

For instance the Provider 5500 system has very low compliance so that occlusions are detected rapidly, but this can be defeated if it is then attached to a

compliant extension tube which will result in a longer time to detect an occlusion, a large stored volume and therapeutic failure. As with any valve it is important that the direction of permitted flow cannot be altered by the patient or untrained staff. One version of the Cardiff valve which changed the direction of flow by rotation of an external tap had this potential problem. Fluid administration sets with an integral anti-reflux valve, used in conjunction with dilute analgesic from the patient controlled-analgesia device, may prove to be the safest and best; e.g. TUTA giving set (Lane Cove, N.S.W.). Finally the characteristics of the administration set with respect to the potential for siphoning have important consequences if not appreciated. The Provider 5500 patient controlled-analgesia pump, which has a dedicated cartridge for administration, can allow fluid to flow freely intravenously when disconnected from the pump. This only occurs with the intravenous mode of patient controlled-analgesia and is compounded when the pump is placed higher than the patient. This potential problem was highlighted by a recent ECRI (Emergency Care and Research Institute) report (*vide infra*) which advocated the use of gate clips when changing cartridges or syringes.

4.6 MONITORING

4.6.1 Equipment

Careful monitoring will prevent the advent of most mishaps with patient controlled-analgesia. The patient needs monitoring for side-effects and efficacy of treatment, as do the pump and delivery system. This can be carried out at several levels in order to optimize safety.

Biomedical engineers, along with anaesthetic technicians, have an important role in pre-installation tests and quality control. All pumps should be bench-tested and should