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# AN ENHANCED PATIENT CONTROLLED ANALGESIA (EPCA) FOR THE EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL)*

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## ABSTRACT

The conventional patient-controlled-analgesia (PCA) can be further improved in terms of less drug consumption and better pain control if advanced feedback control algorithm is applied. The purpose of this research was to develop an enhanced patient-controlled analgesia (EPCA) using a hierarchical fuzzy logic control system with two levels and to apply it to patients in an extracorporeal shock wave lithotripsy (ESWL) operation. The two-level control system utilizes the conventional PCA as a basic level on the top of which is added an adaptive self-learning fuzzy logic control (SLFLC) level. Twenty-three patients involved in these clinical trials were to study the clinical effectiveness of EPCA for the management or pain during the ESWL process. A two-button device was designed, one button for severe pain (SP) and another for mild/moderate pain (MP) to investigate the frequencies of analgesic demands or delivery related to either severe or mild/moderate pain. The results show that the average percentage of demand/delivery to total demand/delivery due to MP is significantly higher than that due to SP, which implies the pain levels that most patients experienced were mostly mild to moderate in the ESWL process with the EPCA. The drug consumption of alfentanil with the EPCA is comparable to that with a fixed FLC; however, it is much lower than that with conventional PCA. In conclusion, the efficiency of the therapy, pain relief, and the patients' satisfaction of pain management with the EPCA in the ESWL operation are superior to those with the conventional PCA.

*Keywords*: Patient-controlled analgesia; Enhanced patient-controlled analgesia; Fuzzy logic controller; Self-learning fuzzy logic control; Extracorporeal shock wave lithotripsy.

## BACKGROUND

Patient controlled analgesia (PCA) has been applied clinically to the pain control for many years and accepted as a valuable method for postoperative pain management.[1,2] Patients who need pain relief simply operate the device by pushing a button which activates an on-and-off drug infusion with a proper bolus. It shares the common benefits of safety with many

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clinical applications of closed-loop control in medicine.[3,4] It has two additional contributions in medical applications: (1) a subjective pain signal is taken using a simple device and (2) the pain signal is further applied to design an on-and-off control. The on-and-off control of drug infusion can achieve a relatively stable pain-relief level, which is the benefit most medical closed-loop controls offer to patient care.[5] However, the rather primitive control algorithm makes patients suffer the fluctuation between the extremes of no pain and severe pain. This problem has not been completely solved by the provision, in some systems, of a constant background infusion of analgesic at a rate determined by medical staff.[6,7] In clinical experience, patients with PCA may result in being drug overdosed, if it is not set up properly.[8,9] The technical primitiveness of the PCA opens up opportunity for further improvement for its clinical effectiveness and patient satisfaction.

To explore the medical applications of the closed-loop control, various control schemes for automatic infusion of drugs have been proposed over the past ten years. These range from simple on/off-type controllers to quite complex model-based controllers. Fuzzy logic control is a simple and effective technique for controlling non-linear and uncertain processes[10] wherein fuzzy logic excels in its tolerance to some imprecision[11] and accommodates uncertainty by utilizing imprecise, qualitative terms such as "low", "medium" and "high". The fuzzy logic controllers also include linguistic control rules, which are easily understood and modified. They have been successfully used for many years;[12–16] however, there are some drawbacks to this design approach. Firstly, the reliable linguistic rules of the control strategy may not always be obtainable. Secondly, some significant process changes may be beyond what the human experience can handle. Thirdly, some process may always have large uncertainty of process parameters (e.g. patients) due to characteristics of inter-patient variation. Therefore, the applications of fuzzy controllers are limited and they need to be enhanced.

An attractive approach to solving these problems is provided by the self-organizing fuzzy logic controller (SOFLC).[17,18] By mimicking the human learning process, the SOFLC control algorithm generates control rules of a system for which there is little knowledge. There have been many studies and applications of SOFLC in recent years, but only a few in biomedical systems. In 1991, Linkens *et al.*[19] published an early study of SOFLC on muscle relaxation, but only in computer simulations. Recently, this has been implemented in clinical trials both in muscle relaxation[20,21] and depth of anesthesia.[22,23] It was found that there are still some problems with the SOFLC algorithm after many applications, mostly in its theory and efficiency.

In order that the control system can be computationally efficient and structurally simple, a self-learning fuzzy logic controller (SLFLC) was used for analgesia in this research. The self-learning mechanism was designed to modify the fuzzy rule base in order that the inter-patient variation can be taken care of. The ultimate goal was stable analgesia with fewer analgesics. The schematic diagrams of the three control systems, i.e. conventional PCA, fuzzy logic PCA (PCA+FLC) and self-learning fuzzy logic PCA (PCA+SLFLC), are shown in Fig. 1.

A fuzzy logic PCA[24] was applied to control the pain in patients during the process of the Extracorporeal Shock Wave Lithotripsy (ESWL) operation whereby the patients experience variable levels of constant pain.[25–27] Its clinical effectiveness was compared with a conventional PCA's. The conventional PCA method let patients control the pain with a pain-driven button, which activates the pump to administer a bolus dose of alfentanil, a rapid onset opioid analgesic, at a fixed time interval (lockout time). Its algorithm uses an initial dose of 0.25 mg and a fixed bolus size of 0.2 mg with a 1 min lockout. The PCA+FLC algorithm uses an initial dose of 0.25 mg, a changeable infusion rate, and a bolus size of 0.1 or 0.05 mg. The infusion rate is adjusted according to a look-up table, which accepts the button pressing history over the last two lockout intervals. The look-up table is designed using fuzzy logic with fixed rules. The bolus size is adjusted according to the button pressing during a lockout interval.

In this research, we investigated the clinical effectiveness of the PCA with SLFLC. It was also applied to patients who underwent the ESWL operation. The PCA+SLFLC algorithm in this paper also used the same initial dose of 0.25 mg and a small bolus size of either 0.1 mg (severe pain) or 0.05 mg (mild/moderate pain) and a changeable infusion rate. The infusion rate, however, was adjusted according to a self-learning mechanism to modify the fuzzy rule base in order to overcome the inter-patient variation. In addition, the analgesic alfentanil was also chosen because of its rapid action and short half-life, both of which are desirable properties for a control agent.

## PATIENTS AND METHODS

This study was approved by the university hospital's Ethics Committee. Twenty three patients, American Society of Anesthesiologist physical status 1 or 2 for

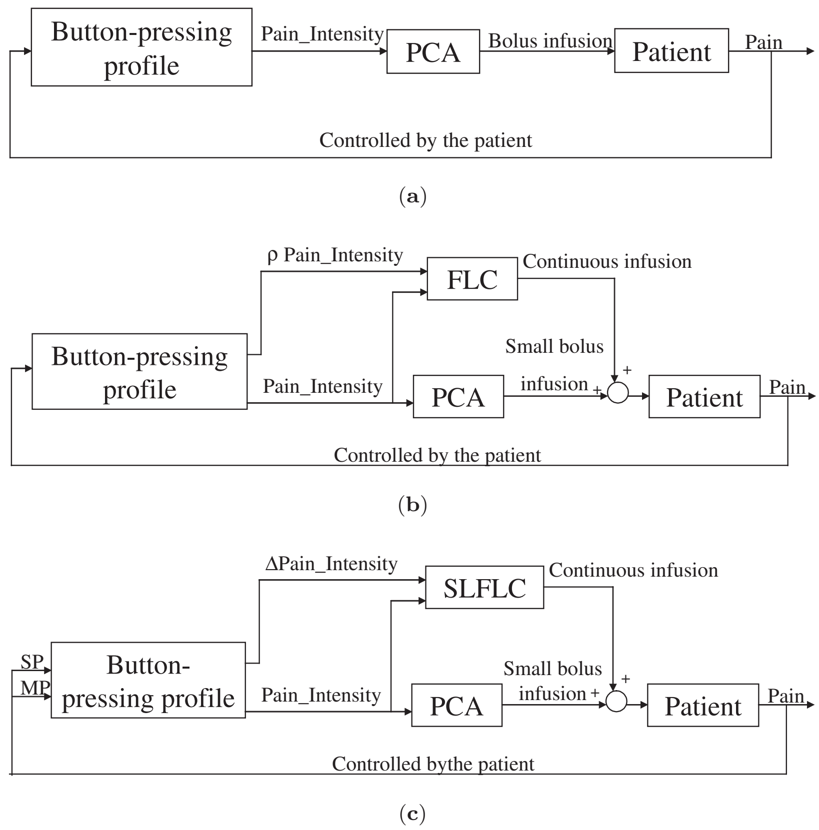



**Fig. 1** The diagrams of the control systems administer alfentanil infusion depending on button-pressing profile of the patient. (**a**) Conventional PCA controller; (**b**) PCA+FLC controller, (**c**) PCA+SLFLC controller.

calculi in the renal pelvis, underwent the ESWL operation using a Lithostar lithotriptor equipped by Simens Nixdorf and were studied. The ESWL is a surgical procedure to remove calculi such that the urinary obstruction or infection can be prevented or cured. The calculi are hard pebble-like stones formed within the body, particularly in the gall bladder (i.e. gallstone) or anywhere in the urinary tract (i.e. cystolithiasis). Calculi in the urinary tract are usually composed of calcium oxalate and are usually visible on X-ray examination. Most of these stones cause pain, whether sited in the kidney, urethra, or bladder; stones passing down a duct (such as the urethra) cause severe colicky pain. In ESWL, used for destroying calculi in the upper urinary tract and gallstones, the shock waves are generated and transmitted by an external power source. The specialized machine used in ESWL consists of a sophisticated radiological system to localize the stone accurately by biplanar X-ray or ultrasound and a shock head or transducer to produce and focus the energy source. The lithotriptor emits variable shock waves to the calculi with variable energies determined by the operator according to the fluoroscopic findings. Patients were excluded if they had clinical evidences of severe respiratory problems, history of drug use, alcohol abuse, chronic pain, a positive pregnancy test, or calculi outside the renal pelvis.

In this study of 23 patients, they were divided into two groups according to whether body weights are taken into consideration during alfentanil administration. The design was to fine tune the drug dosage by multiplying the ratio of patient's weight in kg versus 65 kg for each alfentanil administration in order to compare the difference. The estimated weight of 65 kg was taken from the average weight of 30 EWSL patients according to our preliminary studies. Group A (total 7 patients) used PCA+SLFLC without body weight adjustment while Group B (total 16 patients) used PCA+SLFLC with body weight adjustments. For comparison, the results of this study were analyzed together with those of our previous research[24] using PCA+FLC method defined as Group C, and traditional PCA method defined as Group D. Although taken in different time periods, the operator, the lithotripter and the clinical personnel for the studies were the same group as this study in our medical center. However, it would be better if we were to test different algorithms

**Table 1 The Demographic Clinical Data of the Groups A, B, C, and D.**

| Group | Patient Number | Gender | Age (yr) | Weight (Kg) | Operation Time (min) |
|---|---|---|---|---|---|
| A | 7 | 4F, 3M | 55 (33–70) | 64 (50–72) | 35 (22–45) |
| B | 16 | 8F, 8M | 49 (22–69) | 64 (45–86) | 34 (18–43) |
| C | 13 | 3F, 10M | 47 (25–69) | 67 (52–80) | 45 (34–86) |
| D | 12 | 5F, 7M | 48 (25–71) | 66 (51–91) | 33 (19–53) |

for the same patient. In ESWL surgical operations, it is quite difficult to do so because they are short operations (i.e. average operation time is around 50 min) and patients who return for a second time to do this operation again are quite rare. Data for analysis and comparison include demand frequency during the lock-out interval, the effective drug delivery frequency, and total drug consumptions. The demographic clinical data of these four groups are summarized in Table 1.

## Anaesthetic Control Techniques

Anaesthetic agents were given by staff members, residents or nurse anaesthetists with at least one year experience in anaesthesia. An attending anesthesiologist involved in the study was always present and responsible for standard monitoring of the patient. Also, one investigator who designed this monitoring system was always present and responsible for handling any device or computer malfunction in order to bring the system back in control by the anesthesiologist. After setting up the standard monitors (i.e. systolic arterial pressure (SAP), heart rate (HR), saturated oxygen (SpO2) and respiration rate (RR)), pain intensity was controlled by the PCA+SLFLC method.

The PCA+SLFLC for pain control is a hierarchical controller, which has two levels as shown in Fig. 2, i.e. the basic level (PCA level), and the second level (SLFLC level). Instead of using one pain driven button used in previous study for PCA+FLC, two push-buttons were used in this investigation, one for severe pain (SP) and another for mild/moderate pain (MP), in order that the pain intensity could be detected explicitly.

### *The first level: a PCA level*

This level adopts the PCA method where the patient controls the pain by pressing one of the two pain driven buttons and the pump is activated to administer a bolus dose of analgesic at a fixed time interval (lockout time). In this paper, severe pain (SP), mild/moderate pain (MP), and no pain (NP) of the pain intensity are defined as follows:

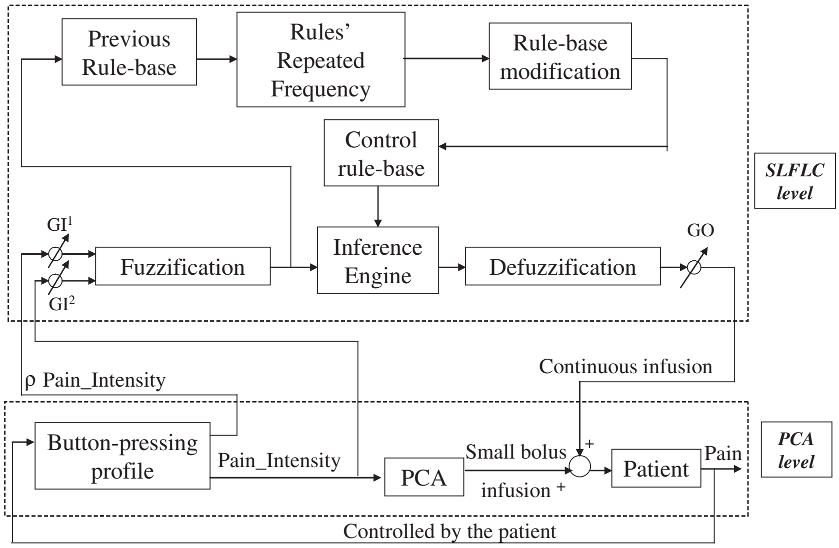
(1) SP: a button is pressed indicating severe pain during a lockout interval
(2) MP: a button is pressed indicating mild/moderate pain during a lockout interval
(3) NP: no button is pressed during a lockout interval

### *The second level: a SLFLC level*

This level includes a simple fuzzy logic controller and a self-learning mechanism. The infusion rate was adjusted according to a look-up table, which accepted the button pressing history over the last two lockout intervals. The look-up table was designed using the self-learning mechanism. The bolus size was adjusted according to the button pressing during a lockout interval. This self-learning mechanism, which supervises the basic level by monitoring its rules' performance, subsequently generated and modified the control rules. Hence, SLFLC is an extension of a simple fuzzy logic controller with the self learning mechanism that incorporates four new functional blocks as shown in Fig. 2: The previous rule-base generation, the rule-base possibility, the rule-base modification algorithm, and the control rule-base performance measure.

The previous rule-base generation
This rule-base can be generated either from expert experience (i.e. anaesthetists) or from learning input and output data. The previous rule-base may have some rules to start with if it begins from expert experience, or may have no rules initially if it starts from zero knowledge. However, after introducing several data into the process, the previous rule-base is modified by each current input and output data. In this paper, we kept the initial rule-base (i.e. 9 rules) from expert experience. Using the previous rule-base from simple FLC instead of performance index was proposed to simplify the controller design.

The rule-base possibility
The use of input-output data from the process to estimate the rules is called logical examination and was proposed by Tong.[28] The quantization of the corresponding measured values produces a sequence of fuzzy sets, such




GI[1] : Input Scaling Factor for the 1[st] input variable GO : Output Scaling Factor for an output variable
GI[2] : Input Scaling Factor for the 2nd input variable

**Fig. 2** The diagram of the control system administers alfentanil infusion depending on button-pressing profile of the patient using a PCA+SLFLC algorithm.

as Positive Big (PB), Positive Medium (PM) *et cetera*, each set of input and output data corresponds to fuzzy sets and performs as a rule. Using the fuzzy set of current data compared to the previous data, it is easy to obtain the rules possibilities.[29] Also, the sliding window technique has been used in this system in order to filter out the previous rules that are less effective than the current rule-base. Modifying the fuzzy rules according to the calculation of the rule possibilities is very simple, easy and a considerable amount of computation time and memory for multi-input and multi-output can be saved.

The rule-base modification algorithm
The method of logic examination can be applied to obtain the conflicting rules. Conflicts can arise in three different ways. They may come from noisy data; they may be a result of unsuitable data quantization; or they may arise because the proposed structure for the model is incorrect. There are two methods to solve the conflicts; one is to delete all the conflicting rules; the other resolves the conflicts by choosing the rule which occurs most often. The latter method has been used in this research. With rules obtained from input and output data, one can calculate the rules possibility for each rule. If there are any conflicting rules, one can compare the rules possibility and retain the one with the largest possibility.

The control rule-base performance measure
After the previous 3 new functional blocks modification, the control rule-base becomes accurate (i.e. no noise contamination). If the performance of the controller is satisfied by the necessary criteria, the rule-base of the controller will stop modification and the rule-base will converge to a constant rule-base.

According to the aforementioned fuzzy logic theory with self-learning algorithm, one can obtain a lookup table to administer the alfentanil. In our system (i.e. PCA+SLFLC and previous research in PCA+FLC[24]), the basic principle of giving an analgesic is that one should use as little of the drug as possible to achieve the required result. Hence, the strategy is always to give a small dose first, judge its effects and then add more as required. In the situation of unknown drug metabolism, it may be better to use even shorter-acting drugs, because if the initial dose causes a problem, at least it will only occur for a short time. Hence, the PCA+SLFLC algorithm in this paper used an initial dose of 0.25 mg and a small bolus size of either 0.1 mg (severe pain) or 0.05 mg (mild/moderate pain) and a changeable infusion rate instead of conventional PCA using the same initial dose of 0.25 mg and a big bolus size of 0.2 mg and no infusion rate. Furthermore, according to pharmacological reasons, the continuous infusion rate of alfentanil will be reduced by 1 ml/h each minute if no pain is pressed. This rule is to guarantee that the patient would not become apneic without pain when drugs are infused continuously. Figure 3 shows a clinical trial from group B (i.e. patient 10) to demonstrate the pain-driven button of demand and delivery records for severe pain (SP) and mild/moderate pain (MP). This

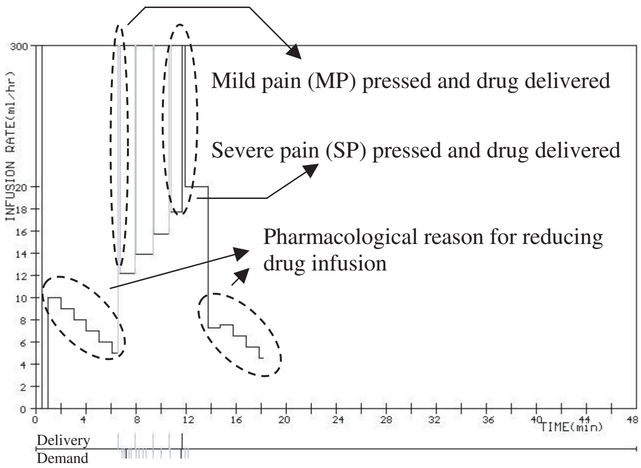



**Fig. 3** Self-learning fuzzy logic control of pain intensity for patient 10 in group B. The solid line is for alfentanil infusion rate, the heavy solid line of bolus is for SP, and the thin solid line of bolus is for MP. The demand and delivery are recorded at the bottom line (i.e. above the line is for delivery and below the line is for demand).

Fig. 3 also shows the drug infusion rate using EPCA and a pharmacological rule to reduce infusion rate when no any pain is pressed.

## Computer, Data Input and Data Output

The whole system was programmed in language "Borland C++". An IBM compatible notebook was used for collection, display, and storage of data. The digital communication was done via RS232 serial ports, which were interfaced to the Datex Dinamap monitor, a pain driven patient controlled two-button box and Graseby 3500 syringe pump for monitoring clinical signs. The monitoring signs were SAP, HR and the button-pressing profile of the patient, as well as infusion rate of analgesic as shown in Fig. 4. Note that the patient could push no button or one of the two buttons, one for severe pain (SP) and another for mild/moderate pain (MP).

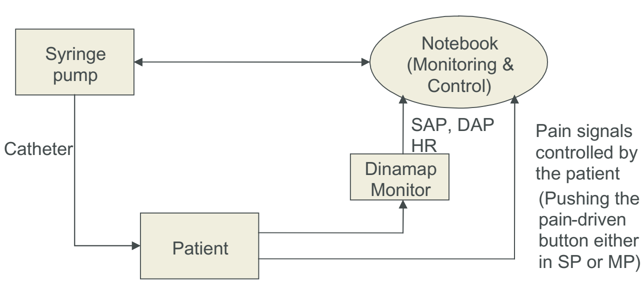



**Fig. 4** The diagram of a PCA+SLFLC controller where the control system administers alfentanil infusion depending on button-pressing profile of the patient either in severe pain (SP) or mild/moderate pain (MP).

In addition, the whole system was still under supervision by the anesthesiologist. The Dinamap monitor was set to provide arterial pressure and heart rate information at $3 \sim 5$ min intervals. The button was pressed by the patient according to adequate instruction given by one investigator who educated the patient on how to push the SP and MP buttons should they feel pain during EWSL therapy. A Graseby 3500 syringe pump provides pumping rates from 0.1 to 1,200 ml/h$^{-1}$ and was controlled by a PCA+SLFLC controller.

## RESULTS

Seven patients defined as Group A using the PCA+SLFLC method without considering patients' body weight and sixteen patients defined as Group B using the PCA+SLFLC method with considering patients' body weight undergoing ESWL operation were studied. A two-button device was used for Groups A and B, and the details of the frequencies of analgesic demands and drug deliveries related to either mild to moderate pain or severe pain could also be studied. The second column of Table 2(a) is the drug demand frequency percentages during the one-minute lock-out interval for mild/moderate pain (MP) alone to total demand frequency in Group A as compared to Group B while the third column of Table 2(a) is for those due to severe pain (SP) alone. The demand frequency percentage mean (SD) due to MP of Groups A and B was 85.71 (24.40) and 77.92 (26.82), respectively. The frequency percentage mean (SD) due to SP of either Group A or Group B was much smaller, 14.29 (24.40) and 22.08 (26.82), respectively. The second column of Table 2(b) presents the effective drug delivery frequency percentages of mild/moderate pain (MP) alone to total delivery frequency in Group A as compared to Group B. The third column of Table 2(b) presents the data due to severe pain (SP). The percentage mean (SD) due to

**Table 2** **The Percentages of Drug Demand and Delivery Frequencies Due to Mild / Moderate Pain and Severe Pain for Groups A and B.**

| Value | MP (%) | SP (%) |
|---|---|---|
| (a) Demand frequency | | |
| Group A ($n = 7$) | $85.71 \pm 24.40$ | $14.29 \pm 24.40$ |
| Group B ($n = 16$) | $77.92 \pm 26.82$ | $22.08 \pm 26.82$ |
| (b) Delivery frequency | | |
| Group A ($n = 7$) | $85.71 \pm 24.40$ | $14.29 \pm 24.40$ |
| Group B ($n = 16$) | $78.09 \pm 27.88$ | $21.91 \pm 27.88$ |

MP, mild/moderate pain; SP, severe pain; $n$; patient number.

Values are expressed as mean $\pm$ SD.

MP of Groups A and B was 85.71 (24.40) and 78.09 (27.88), respectively. The percentage mean (SD) due to SP of Groups A and B was again small, 14.29 (24.40) and 21.91 (27.88), respectively. In summary, Table 2 has shown for both Groups A and B that the average percentage of demand/delivery to total demand/delivery due to MP is significantly higher than that due to SP. That means the pain that most patients experienced was mild to moderate in the process. After the drug had been controlled by the hierarchical controller, the pain level was reduced to a no pain (NP) level. That means serum alfentanil drug concentration can be achieved as close as the analgesia level when using the PCA+SLFLC method. Hence, the strategy of drug administration is always to give a small dose first, judge its effects and then add more as required. However, if one method of control gave more drugs and these drugs resulted in less pain, they may have strong side effects, such as depression SAP and HR or even worse of apnea. This should be avoided in PCA drug administration. In our system, no apnea or remarkable respiratory depression were noted in our patients as monitored by pulse oximetry (SpO2) and respiratory rate (RR). Also, no remarkable high or low values of SAP, DAP, and HR for these vital signs were noted as monitored by Datex Dinamap monitor of each patient. Therefore, it would be logical to look into the reduction of the drug consumption in the ESWL process because the mild to moderate pain signal activates the pump to administer analgesic at a smaller infusion rate.

Patients in our previous research[24] using the PCA+FLC method was defined as Group C, and those using traditional PCA method was defined as Group D. Table 3 shows the alfentanil drug consumption (DC), the frequencies of analgesic demands (DF), and the ratios of drug delivery frequency to analgesic demand frequency (D/D ratio). The mean (SD) of drug consumption of A, B, C, and D groups was 16.49 (10.07), 21.08 (15.20), 18.72 (9.25) and 41.34 (17.99) $\mu g \cdot kg^{-1} h^{-1}$, respectively. The mean (SD) of frequencies of analgesic demands of A, B, C, and D groups was 0.17 (0.25), 0.28 (0.38), 0.17 (0.13), and 0.45 (0.41) $\min^{-1}$, respectively. The percentage mean (SD) of the ratios of drug delivery frequency to analgesic demand frequency of A, B, C, and D groups was 79 (28)%, 73 (26)%, 82 (19)%, and 60 (26)%, respectively. Less drug consumption together with more effective delivery for mild/moderate pain button push represents a better control technique for pain management. Less drug consumption means less drug overdose and side-effects, more mild/moderate pain button pushes mean less painful experiences, greater ratio of effective drug delivery frequency to analgesic demand frequency is strongly related to better patients' satisfaction and pain relief. Therefore, the results have shown that the PCA+SLFLC method either with or without body weight consideration for alfentanil administration (i.e. Groups A and B, respectively) and PCA+FLC method (i.e. Group C) are more effective than the traditional PCA method (i.e. Group D). Not only are the amount of drug and the frequency of analgesic demand lesser but also the ratio of drug delivery frequency to analgesic demand frequency is higher. However, the three groups of A, B, and C present no significant differences with regard to the alfentanil drug consumption, the frequency of analgesic demands, and the ratio of drug delivery frequency to analgesic demand frequency. In addition, no apnea or remarkable respiratory depression was noted in our patients as monitored by pulse oximetry (SpO2) and respiratory rate (RR). Also, no remarkable high or low values of SAP, DAP, and HR for these vital signs were noted in our system as monitored by Datex Dinamap monitor of each patient as shown in Fig. 5 from one clinical trials (i.e. patient 1 of Group B).

## DISCUSSION

In this paper, a two-button device was used for Groups A and B patients to express their pain intensity, in comparison to one-button devices used in previous research (Group C) and traditional PCA of Group D. The results

**Table 3 The Drug Consumption (DC), the Frequencies of Analgesic Demands (DF), and the Ratios of Drug Delivery Frequency to Analgesic Demand Frequency (D/D Ratio) of Alfentanil Undergoing ESWL Surgery for Groups A, B, C, and D.**

| | Groups | | | |
|---|---|---|---|---|
| **Value** | **A ($n=7$)** | **B ($n=16$)** | **C ($n=13$)** | **D ($n=12$)** |
| DC ($\mu g \cdot kg^{-1} \cdot h^{-1}$) | $16.49 \pm 10.07$ | $21.08 \pm 15.20$ | $18.72 \pm 9.25$ | $41.34 \pm 17.99$ |
| DF ($\min^{-1}$) | $0.17 \pm 0.25$ | $0.28 \pm 0.38$ | $0.17 \pm 0.13$ | $0.45 \pm 0.41$ |
| D/D ratio (%) | $79 \pm 28$ | $73 \pm 26$ | $82 \pm 19$ | $60 \pm 26$ |

Values are expressed as mean $\pm$ SD, $n$ is the patient number.

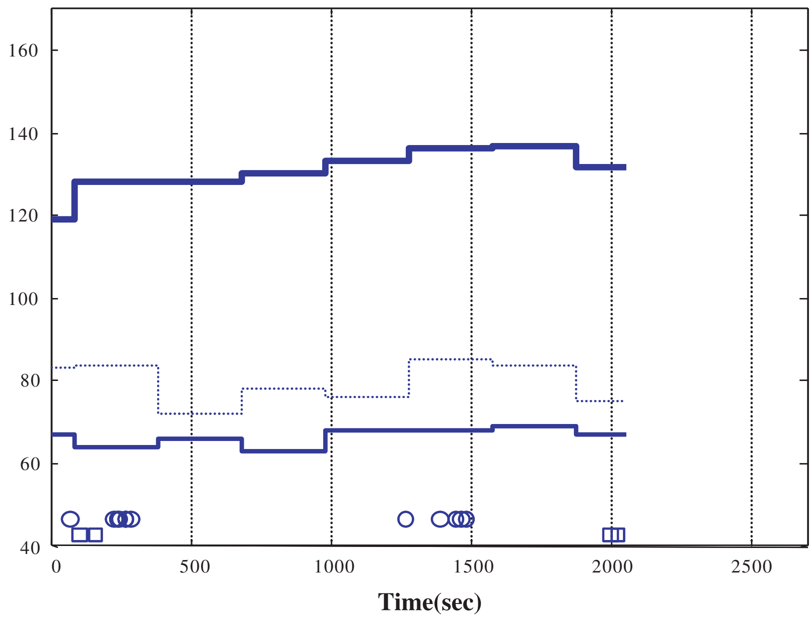



**Fig. 5** Vital signs and pain-driven of SP and MP for patient 1 in group B. The heavy solid line is for SAP, the light solid line is for DAP, and the dot line is for HR. The pain-driven button is recorded at the bottom (i.e. circle is for pressing SP and square is for pressing MP).

were able to show the quality of pain control in terms of differentiating the pain signals of either mild to moderate or severe. Both the percentages of analgesic demand frequency and drug delivery frequency shows that mild to moderate pain possesses a greater portion of analgesic demands and drug deliveries than the severe pain does. That means most pain signals during the operation are mild to moderate and the drug consumption can be significantly reduced. For safety reasons, the operators want the patient to be conscious during ESWL procedure so that the patients response could be taken as a guide for operation and to avoid complications of organ injury. Therefore, if the pain can thus be controlled at either above or under a little bit of the threshold of the pain level, not only can it provide a good clinical situation for the operators but also it can achieve a more stable analgesia level. In contrast, the traditional PCA method has shown otherwise that serum alfentanil drug concentration varies very widely between pain and sedation level.

The results of this study have also shown that both PCA+SLFLC methods (i.e. Groups A and B) and PCA+FLC (i.e. Group C, previous research) are more effective than the traditional PCA method (i.e. Group D). Not only are the amount of drug and the frequency of analgesic demands significantly less than the PCA method but also the ratio of drug delivery frequency to analgesic demand frequency is significantly higher than the PCA method. However, the three groups of A, B, and C have no significant difference with regard to the alfentanil drug consumption, the frequency of analgesic demands, and the ratio of drug delivery frequency to analgesic demand frequency. This may be caused by the short operation time because the average operation time of Groups A and B was 35 and 34 min, respectively. The learning process in self-learning level has not been long enough so that most of the rules were still derived from previous rule-base. Therefore, from the clinical point of view, the more suitable cases would be for cancer pain using PCA as pain management. It takes a much longer procedure than ESWL in clinical trials. Another approach is doing the simulation. Then, SLFLC can be validated in either longer clinical procedures or longer simulations. Obviously, using the computer simulation it would be easier to test self-learning level for a longer process application. Therefore, a patient model of the pain intensity scale will be built in the next stage of development. In the past, it was generally considered that a complicated mathematical approach could model a system more accurately. But, this view has problems with ill-defined, complicated and nonlinear systems. Recently, many studies have investigated this field from the point of view of artificial intelligence. Linkens and Nyongesa[30,31] applied a genetic algorithm to either off-line or on-line acquisition of fuzzy rules and membership function for multi-variable fuzzy control. Muthuswamy and Roy[32] applied a neural network based on fuzzy integrals and bispectral analysis of electroencephalograms (EEG) in order to predict depth of anaesthesia. Zhang and Roy[33] proposed a derived fuzzy knowledge model for estimating the depth of anesthesia. Recently, Shieh *et al.*[34–36] applied an artificial neural network or genetic fuzzy modeling by utilizing their self-learning properties to model the patient using bispectral index and vital signs. However, it is still very difficult to judge which method is best, and the application of these intelligent methods is strongly dependent on different systems situations.

Fuzzy logic is an appropriate, simple and effective technique for controlling non-linear and unpredictable processes, dealing in imprecise, qualitative (i.e. fuzzy) terms such as low, medium or high rather than precise measurements. This imprecision allows simple but effective control rules to be generated which are easy to modify and update rapidly in real-time. Using a fixed rule-base, we have demonstrated previously that fuzzy logic control is appropriate for controlling patient-controlled analgesia.[24] In this paper, by incorporating a self-learning layer to the fuzzy logic controller, self-learning was performed real-time in the clinical situation. It has been argued that it is unsafe to start control with a blank rule-base, because the process output value may move to a region of the fuzzy rule-base where no control rule is available for execution. Our self-learning hierarchical controller starts with a previous fuzzy logic controller rule-base in order to make sure that it is safe to start. Also, using previous rule-base from simple FLC instead of performance index was to simplify the controller design because the unclarity of the rule learning from performance index has limited the application of SOFLC over a wide area. Moreover, modifying the fuzzy rules according to the calculation of the rule possibilities is very simple and easy, and a considerable amount of computation time and memory for multi-input and multi-output can be saved. This is the first study to investigate the clinical application in PCA of such an hierarchical control structure.

The self-learning strategy implemented in our hierarchical controller functioned by rapidly and repeatedly measuring pain intensity controlled by the patient and modifying the alfentanil continuous infusion rate and bolus amount as well. This allows the controller to recognize the patient's drug requirements and select infusion rates and bolus amount in order to alleviate pain. Initially, the fuzzy rule-base (i.e. 9 rules from anesthesiologists) used in previous research[24] was adopted for the rule-base. The first new rule is simple and generated by assessing the return of pain intensity (Pain_Intensity) and the change of pain intensity ($\Delta$Pain_Intensity) towards the change of alfentanil infusion rate ($\Delta$Flow_Rate) to control pain. The effect is then assessed and adapted by generating new rules as control continues. This is achieved by calculating the rule possibilities from the previous rule-base and new rules and modifying recently generated control rules due to the self-learning function of the controller. In addition, an aging process (i.e. a sliding window) was added to the rules generated so that the recently generated carries more weight, or are considered more relevant than older rules. This helps eliminate steady error and continually improves controller's performance. Hence, in this paper, we kept the initial rule-base (i.e. 9 rules) and just allowed another 6 new rules to be generated. Therefore, the maximum number of rules is 15 if they are all different and the minimum number of rules is 9 originated from the initial rule-base. According to our experience, if the rules are too many, the change of alfentanil infusion rate will become too small which then slows down the controller performance.

Pain is inherently subjective and pain measurement relies primarily on the verbal report of patients. Furthermore, pain is a complex, private experience and attempts to make valid assessments of it have been fraught with difficulties.[37] Thus, the wide variation in the pain experience among individuals leads to a large variability in the pain scale ratings of patients who experience similar stimuli or interventions. In addition, pain scale measurements are often interpreted in different ways by different researchers and clinicians, depending on the criteria they choose to apply.[38] The extent of painful response, e.g. VAS, is not entirely determined by the nociceptive stimuli but rather as a result of both sensory-discriminative and emotional-cognitive components of the patient's suffering.[39] Moreover, pain has recently become the "fifth vital sign" to be entered into a patient's chart along with temperature, blood pressure, pulse and respiration rates.[40,41] Hence, how to model this pain pattern to be more objective and reliable in order to continuously monitor this fifth vital sign is the most important aspect of the pain measurement.

Although pulse-oximetry for oxygenation (SP02) and respiration rate (RR) are routinely monitored for patients' safety, especially for overdose-induced apnea or respiratory depression, they are not included as pain signal inputs in this study. The usefulness of these two additional parameters for assessing pain level remain to be studied. The changeable infusion rate which was adjusted according to a look-up table designed using fuzzy logic with fixed rules may interfere with the interpretation of our results, e.g. less button push with higher infusion rates. In this regard, the meaning for frequencies may be misleading. The significance of less analgesic demand frequency of button push itself, however, may represent that the level of analgesia is better controlled with fuzzy logic controller by providing more reasonable continuous infusion rates. Because drug consumptions are concomitantly greatly reduced, it is unlikely that overt continuous infusion rates make up the differences. Although studies (Groups C and D) were taken in different time periods, the staff, the machine and the operating urologists and assistance were from the same group with the same standard operating procedure (SOP), therefore we believe that the influences and differences were minimal, if any.

## CONCLUSIONS

An enhanced PCA (EPCA) with a hierarchical architecture control was developed in this study and applied to patients undergoing ESWL operation. It includes two levels, which are the basic level (i.e. PCA level) and second level (i.e. SLFLC level). We attempted to merge the relative strengths of the each technique to achieve beneficial synergy in the generation of a generic controlling system applied in PCA. In this paper, 23 patients were recruited in clinical trials. Most of the pain signals are mild to moderate pain signals from their direct feedback and the drug consumption was greatly reduced. The pain level was reduced to no pain level which means serum alfentanil drug concentration can be achieved as close as the analgesia level. Based on the results of our previous and current research, we have reached a conclusion that both PCA+SLFLC and PCA+FLC methods are more effective than the traditional PCA method. Not only are the amount of drug consumed and the frequency of analgesic demands lesser but also the ratio of drug delivery frequency to analgesic demand frequency is higher than those in the conventional PCA method. It can be concluded that the quality of the pain management with the EPCA in the ESWL operation is superior to that with the conventional PCA. However, the difference of PCA+SLFLC and PCA+FLC methods was not seen from the clinical trials and more studies are needed. One possible approach is to build a pain model of the patient via either fuzzy model or artificial neural networks by utilizing their self-learning properties. Our future plan includes continuing research towards the above synergetic design techniques for both simulation and clinical trials.

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