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Research Article

Efficacy and side effects of small versus large bolus size morphine patient controlled analgesia combined with paracetamol

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Abstract *Introduction:* Patient controlled analgesia (PCA) provides a better analgesia over conventional opioid treatment. The reduction of bolus size and its efficacy on pain relief and associated side effects were not enormously studied. This study was constructed to evaluate small versus traditional bolus size PCA, including pain relief, and side effects of both regimens.
Methods: Seventy-seven patients were included in the study. All patients received general anesthesia. Patients were randomly distributed between two groups; traditional group (M1) received a bolus dose of Morphine as 0.02 mg/kg body weight to a maximum of 1.5 mg, and group (M2) where 0.01 mg/kg body weight to a maximum of 0.75 mg is the bolus dose. PCA machines were set up at 6 min lockout interval and a maximum dose of 0.15 mg/kg/h to a maximum of 10 mg/h. Rescue doses were given according to pain scores and reported. 1000 mg Paracetamol every 6 h were given. Morphine consumption at 24 and 48 h, VAS at 1, 2 then every 4 h for 48 h were measured. Reported complications as respiratory depression, over sedation, constipation, pruritus, nausea and vomiting were analyzed.
Results: Morphine consumption in small bolus size group M2 during the first (36.38 ± 17.75) and second 24 h (30.22 ± 17.15) were less when compared to large bolus size group M1 (39.20 ± 17.97

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and 36.38 ± 17.75), the change was insignificant. In spite of using small bolus size Morphine in group M2, pain scores were close to group M1 and statistically insignificant. The frequency of occurrence of side effects was statistically insignificant when comparing the two groups.

Conclusions: Small bolus size of Morphine PCA produces efficient pain relief but does not reduce total morphine consumption nor did morphine associate side effects.

1. Review of literature

Systemic use of opioids for control of pain following orthopedic surgery is common and a meta-analysis results show that patient controlled analgesia (PCA) provides a better analgesia than conventional opioid treatment [1]. Combined use of paracetamol and morphine for treatment of postoperative pain has been studied before in certain procedures. In some studies this combined regimen can reduce the total dose of analgesics and minimize the adverse effects, however in other studies, morphine sparing effect did not result in parallel reductions in opioid-related adverse effects [2–4] or narcotic requirements. Respiratory depression and other opioids side effects like nausea, vomiting and pruritus are a major concern of PCA usage. Some major studies including over 10,000 patients suggested significant PCA associated respiratory depression requiring intervention, to occur in a range of 0.2% [5]. Respiratory depression and other opioids side effects were related to the total consumption. Few studies were published about reduction of bolus size and its efficacy on pain relief and associated side effects; the results were incorporate [6,7]. In the present study the investigators hypothesized that perioperative combined use of intravenous paracetamol and PCA morphine may result in decreasing the bolus size and hence opioid associated side effects. The primary aim of this study is to study pain relief using small versus traditional large bolus size PCA. The secondary aim is to study and compare between side effects of both regimens.

2. Methods

After informed patient consenting, minimum of 72 patients scheduled for abdominal surgeries with skin incision – 15 cm and total hip or knee replacement, were included in a randomized, single-blinded, placebo-controlled study.

The sample size is based on other study [6], comparing the change in morphine consumption between the two groups, a power of 0.80, significance criterion of <0.05, estimated standard deviation of 10 and a minimum expected difference of 50. Patients on any opioids, less than 18 year or more than 60 year old and who are allergic to Morphine or Paracetamol were excluded from the study.

All patients received general anesthesia with Propofol 2 mg/kg and fentanyl 2 mcg/kg at induction, and maintained on Sevoflurane and fentanyl infusion 2 mcg/kg/min. In PACU, rescue doses of Morphine (0.2 mg/kg) were used divided on four doses every 6 min until pain is controlled and VAS below 3. Patients were randomly distributed between two groups using computer program, traditional group (M1) where patients received a bolus dose of Morphine as 0.02 mg/kg body weight to a maximum of 1.5 mg using PCA machine and 0.01 mg/kg body weight to a maximum of 0.75 mg in small dose group (M2) [8]. Patients started using PCA machine CAD Solis, USA, with a computerized self reporting system before discharging from PACU at 6 min lockout interval and a maximum dose of 0.15 mg/kg/h to a maximum of 10 mg/h. All patients have a patent intravenous line with crystalloids running at 50–100 ml/h and monitored by continuous pulse oximetry.

PCA bolus dose was increased by 0.5 mg at anytime to a maximum of 2 mg, if pain was persistent with VAS more than 4 and after 2 rescue doses of 2.5 mg Morphine using the PCA machine. This was done by acute pain service (APS) physician who was blinded to the study and according to APS and hospital policy. Respiratory depression with oxygen saturation less than 90% and/or over sedation are treated with intravenous Naloxon 0.4 mg in divided doses when required together with decreasing the PCA bolus dose by 0.5 mg. All patients received regular doses of 1000 mg Paracetamol every 6 h starting 15 min before skin closure and a prophylactic dose of grainsetron 1 mg for nausea and/or vomiting. Measurements included total Morphine consumption in 24 h and 48 h, VAS after 1, 2 then every 4 h for 48 h. Complications as respiratory depression defined as oxygen saturation less than 90%, over sedation (Ramsay sedation score more than 3) [9], constipation, pruritus, nausea and vomiting were recorded. Measurements will be recorded via PCA machine CAD Solis, USA, with a computerized self reporting system and reported by a blind observer.

3. Results

Seventy-seven patients were included in the study after excluding 4 patients due to missing data. 40 patients were included in traditional (M1) group, and 37 patients in small dose (M2) group. Table 1 reflects changes in the demographic data where there were no significant changes between the two studied groups in age, sex, body weight and surgical procedures.

Nevertheless the consumption of Morphine in small bolus size group M2 during the first (36.38 ± 17.75) and second 24 h (30.22 ± 17.15) were less when compared to large bolus size group M1 (39.20 ± 17.97 and 36.38 ± 17.75), the change was insignificant (Table 2).

In spite of using small bolus size Morphine in group M2, pain scores were close to group M1 and statistically insignificant (Fig. 1).

Table 3 represents the frequency of occurrence of side effects which were statistically insignificant when comparing the two groups by using Fisher exact test.

4. Discussion

In the present study, the use of small bolus dose has lead to efficient pain relief with less but insignificant decrease in Morphine consumption. The side effects were close and statistically insignificant between the two studied groups.

Table 1 Demographic data.

	Group M1 (n = 40)	Group M2 (n = 37)
Age	41.03 ± 16.19	44.05 ± 18.89
Weight	79.18 ± 12.60	78.43 ± 11.53
Sex F/M	18/22	22/15
Abdominal surgery	20	19
Total hip replacement	11	10
Total knee replacement	9	8

Values are mean ± standard deviation.
Group M1 = patients receiving large bolus dose of PCA morphine.
Group M2 = patients receiving small bolus dose of PCA morphine.

Table 2 Bolus dose and Morphine consumption (mg) at 24, 48 h.

	Group M1 (n = 40)	Group M2 (n = 37)	t-Test (p)	Group M1 paired t (each two consecutive) (p)	Group M2 paired t (each two consecutive) (p)
Bolus dose	1.27 ± 0.34	0.73 ± 0.16	8.79* (<0.001)		
Morph 24 h	39.20 ± 17.97	33.46 ± 18.23	1.39 (0.168)		
Morph 48 h*	36.38 ± 17.75	30.22 ± 17.15	1.53 (0.130)	6.46* (<0.001)	8.03* (<0.001)

Results are expressed as mean ± SD.
Group M1 = patients receiving large bolus dose of PCA morphine.
Group M2 = patients receiving small bolus dose of PCA morphine.
* p values < 0.05 are considered significant.

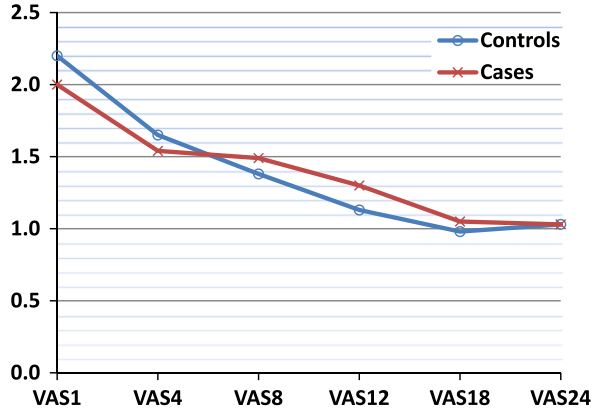

Figure 1 Pain assessment at 1, 4, 8, 12, 18 and 24 h by visual analogue scale (0 = no pain, 10 = severe pain) between group M1 (control) and group M2 (cases).

Measuring the amount of rescue analgesic required to treat postoperative pain can be used for the assessment and comparison of pain relief effect of analgesics. PCA allows patients to titrate the dose of analgesic needed for adequate pain relief by themselves. In addition, the numbers of attempts are used for assessment of proper analgesia.

In the present study, the efficacy of analgesia was not assessed by the number of missed attempts since PCA machine CAD Solis, USA, handles are supported with green light to indicate the readiness for firing and a red light indicating that the machine is in lockout period.

Pain relief efficacy was assessed by VAS which was efficient in the two studied groups (Fig. 1) with insignificant difference. This adequate analgesia in spite of using reduced bolus size in group M2 (0.73 ± 0, 16 vs. 1.27 ± 0.33 mg) is interesting. Low pain scores in group M2 with small bolus Morphine can be explained by analyzing total Morphine consumption in the first and second 24 h. The consumption was less in group

Table 3 The frequency of side effects.

	Group M1 (n = 40)	Group M2 (n = 37)	p value
Sedation	1 (2.5%)	2 (5.4%)	0.605
Respiratory depression	0	1 (2.7%)	0.481
Constipation	0	1 (2.7%)	0.481
Pruritus	2 (5%)	0	0.494
N and V	8 (20%)	6 (16.2%)	0.771

* p Values < 0.05 are considered significant.
Results are expressed as number (%).
Group M1 = patients receiving large bolus dose of PCA morphine.
Group M2 = patients receiving small bolus dose of PCA morphine.

M2 but statistically insignificant when comparing the two studied groups (39.2 ± 17.9 vs. 33.4 ± 18.2 mg) in the first 24 h and (36.4 ± 17.7 vs. 30.22 ± 17.15) after 48 h.

The results go with the study done by Morlion et al. [6] when the authors used a reduced bolus size of patient controlled analgesia; there were no significant decrease total consumption or side effects.

From other studies we know that Paracetamol is an effective adjunct to opioid analgesia, opioid requirements being reduced by 20–30% when combined with a regular regimen of oral or rectal paracetamol [10]. The use of oral paracetamol in higher daily doses (1 g every 4 h) in addition to PCA morphine lowered pain scores, shortened the duration of PCA use and improved patient satisfaction [11]. Meta-analyses looking at paracetamol as an adjunct to PCA opioids also showed that PCA morphine requirements were decreased but there was no improvement in pain relief or decrease in opioid-related adverse effects [4,12]. In the present study, Paracetamol was used as adjuvant drug to Morphine in order to decrease the total Morphine requirements.

When studying PCA associated side effects, no patients required mechanical ventilation because of excessive respiratory depression and persistent low oxygen saturation. Inspite of the small bolus size in group M2, one patient had oxygen saturation less than 90% and treated with oxygen and 0.2 mg Naloxon; this change was statistically insignificant when compared to patients in group M1.

However, the number of patients with a peripheral oxygen saturation below 90% varied somewhat between the studies; the variation may simply be a result of different timetables for the measurements in each study. In a Clinical study including a large sample size of over 10,000 patients, the incidence of significant respiratory depression requiring intervention was 0.2% [5] and 1.2–11.5% in Dolin and Cushman study [13].

Postoperative nausea and vomiting is one of the most frequent complications after pain in the postoperative period. The incidence in the present study varied from 19.5% in group M1 to 15.8% in group M2. No significant reduction in postoperative nausea and vomiting was seen between the two studied groups.

Dolin and Cashman in their review of patient tolerability to PCA, suggested that there may be differences in the clinical setting and they reported means for complications following PCA: nausea 32%, vomiting 20.7%, pruritus 13.8% and excessive sedation 5.3% [13].

5. Conclusions

Small bolus size of Morphine patient controlled analgesia produces efficient pain relief but does not reduce total morphine consumption or morphine associate side effects.

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