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How effective is periarticular multimodal drug injection in open elbow arthrolysis? A prospective double-blind randomized controlled trial

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Background: Evidence on the efficacy and safety of periarticular multimodal drug injection (PMDI) in open elbow arthrolysis (OEA) is limited. This study aimed to investigate differences in postoperative pain, blood loss, and range of motion (ROM) between PMDI vs. no injection among patients undergoing OEA, and the presence of PMDI-related complications.

Methods: This prospective, double-blind randomized controlled trial included 59 patients who underwent OEA. Patients randomly received PMDI (ropivacaine, epinephrine, ketoprofen) before wound closure or no injection. The primary outcomes were elbow pain over the first postoperative week at rest and during motion, measured using the visual analog scale (VAS). VAS scores were compared to attain the 20-mm threshold values for a minimum clinically important difference. Parecoxib consumption on OEA night and postoperative days (PODs) 1-3 and total consumption during the first postoperative week were recorded. Blood loss was recorded every 24 hours until POD 3. ROM during rehabilitation was measured daily from day 1 to day 7 after surgery, as well as at 3-month follow-up. Medication-related side effects were recorded prospectively.

Results: The mean VAS score showed clinically important differences between PMDI and control groups at rest on OEA night (mean difference [MD], 25 mm; $P < .001$) and first 3 PODs with motion (POD 1: MD, 28 mm, $P < .001$; POD 2: MD, 21 mm, $P < .001$; POD 3: MD, 21 mm, $P < .001$) but not in other postoperative assessments. Parecoxib consumption was lower in the PMDI group on OEA night and PODs 1-3. Total parecoxib consumption during the first postoperative week was lower in the PMDI group vs. the control group (MD, 148 mg; $P < .001$). Blood drainage was less in the PMDI group vs. the control group on POD 1 (MD, 38 mL; $P = .016$) but not on POD 2 ($P = .950$), POD 3 ($P = .259$), or total ($P = .184$). The PMDI group exhibited significantly better ROM during the first 4 PODs than the control group, whereas there was no difference at 3-month follow-up. No medication-related side effects were noted in the PMDI group.

Conclusion: PMDI effectively relieves pain and reduces analgesic consumption for OEA patients, without an apparent increase in risks.

Level of evidence: Level I; Randomized Controlled Trial; Treatment Study

Keywords: Open elbow arthrolysis; periarticular multimodal drug injection; visual analog scale for pain; parecoxib; blood loss; range of motion

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It is considered the "fifth vital sign" and one of the most primitive fears of surgical patients.[22] More than 30% patients undergoing major upper extremity surgeries reported moderate-to-severe pain,[17]

The study protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital East Campus (approval no. 2019014).

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which affects joint function recovery, prolongs hospital stay, increases medical costs, interferes with sleep, and may even provoke intractable chronic pain, causing great detriment to normal daily life.[5] As Morrey[14] noted, "failure to provide adequate analgesia impedes early physical therapy and rapid rehabilitation…"; obviously, perioperative analgesia in orthopedic surgery is very necessary.

Post-traumatic elbow stiffness (PTES) is a kind of disease that patients lose partial or entire movement in their affected elbow after trauma, with an incidence as high as 56%.[2] PTES causes severe limb disability, and patients even lose self-care ability such as eating, dressing, and personal hygiene, which greatly increases the burden on family and society.[28] Surgery is indicated if function fails to improve with 6 months' conservative therapy. Open elbow arthrolysis (OEA) is the most commonly reported treatment method and has been proven effective.[27] However, little research has been performed on the perioperative analgesia of OEA.

Periarticular multimodal drug injection (PMDI, or cocktail injection) has been described as the systematic injection of multimodal analgesic agents into the capsule, ligaments, muscles, and other soft tissues during surgery. The main agents used are long-acting local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and epinephrine with or without corticosteroids. After an early report of its application in total knee arthroplasty (TKA),[3] this technique has gained the surgeon's attention for its simplicity and effectiveness, with better pain relief, less opioid consumption, and lower rates of nausea and vomiting compared with management without PMDI.[11] PMDI has been reported to have similar efficacy in sports medicine[8] and trauma.[13] No significant differences were also found in anesthesia effects between PMDI and other analgesic methods like peripheral nerve block, which indicates to be a safer, cheaper, and more convenient alternation.[1]

However, to the best of our knowledge, no study has reported the efficacy and safety of PMDI application in OEA. In this prospective, double-blind randomized controlled trial (RCT) comparing PMDI (using local anesthetics, NSAIDs, and epinephrine) with no PMDI for OEA, we aimed to answer the following questions: (1) Does postoperative pain differ between patients who received PMDI vs. no injection? (2) Are there any differences in postoperative blood loss or range of motion (ROM) between the 2 groups? (3) Are there any medication-related side effects in the PMDI group?

Methods

This was a single-center RCT in which patients undergoing OEA randomly received PMDI or no injection. Written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment at http://www.chictr.org.cn (ChiCTR1900021564). The work has been reported in line with Consolidated Standards of Reporting Trials guidelines.

Patients scheduled for OEA between March 1 and May 31 of 2019 were eligible for inclusion. Exclusion criteria were stiffness caused by nontraumatic factors, age <18 or >65 years, regular narcotic use, psychiatric or dementia illness, medication allergy, hepatic or renal dysfunction, asthma, and prolonged QT interval on electrocardiography. A total of 72 patients underwent OEA during the study period and were eligible for inclusion. Among them, 13 patients were excluded, including 5 with stiffness caused by nontraumatic factors, 4 with age <18 and 1 with age >65 years, and 3 refused to participate. The Consolidated Standards of Reporting Trials flow diagram is shown in Figure 1.

The remaining 59 patients were randomly assigned to the PMDI group or the no injection (control) group. Randomized numbers ranging from 0 to 99, generated using Microsoft Excel (Redmond, WA, USA), were placed in an opaque envelope. Before surgery, unblinded allocating staff, who did not participate in outcome assessment, selected a sealed envelope in the operating suite. Patients with even numbers received PMDI, and those with odd numbers did not receive injection. Ultimately, 28 patients received PMDI, whereas the remaining 31 received no injection; no patient received any other pre-emptive multimodal medication. Table I summarizes patients' demographic and baseline clinical characteristics.

Injections were performed just after completion of OEA and before closure. The PMDI solution contained 10 mL of 10 mg/mL ropivacaine, 15 mg of ketoprofen, and 0.1 mL of 1.0 mg/mL epinephrine, based on a formulation published by the Mayo Clinic.[1] These agents were mixed with normal saline to a combined volume of 60 mL, which were evenly divided for injection: 20 mL into the medial and lateral collateral ligaments, 20 mL into the triceps and flexor muscle-tendon units, and the remaining 20 mL into the incision site.

Sufentanil at 100 mg was placed in a continuous intravenous infusion device and administered to all patients during the first 2 days after surgery for conventional pain relief. The analgesic was given at 2 mg/h, with a maximum dose of 48 mg in a 24-hour period. All patients were prescribed celecoxib (200 mg orally, twice daily) postoperatively to prevent heterotopic ossification and for pain remission.[24] No other oral medication, intravenous patient-controlled analgesia, or single or continuous peripheral nerve blockade was used for pain control after surgery. For rescue analgesia, 40 mg of parecoxib was administered intramuscularly.

All surgeries were performed by the same surgeon through a standard procedure.[26] The postoperative hospital stay was 1 week uniformly. In this week, all patients were treated by the same physical therapist and started an exercise program on postoperative day (POD) 1. Postoperative exercises consisted of circuits of "active, assisted, and passive" elbow flexion and extension movements, with 30 on the first day, increased by 30 per day.[25]

Outcome measurements

The primary outcome was elbow-pain evaluation over the first postoperative week. Patients were instructed to draw a mark on the line that represents the intensity of the pain they felt. The visual analog scale (VAS) score was determined by the distance between

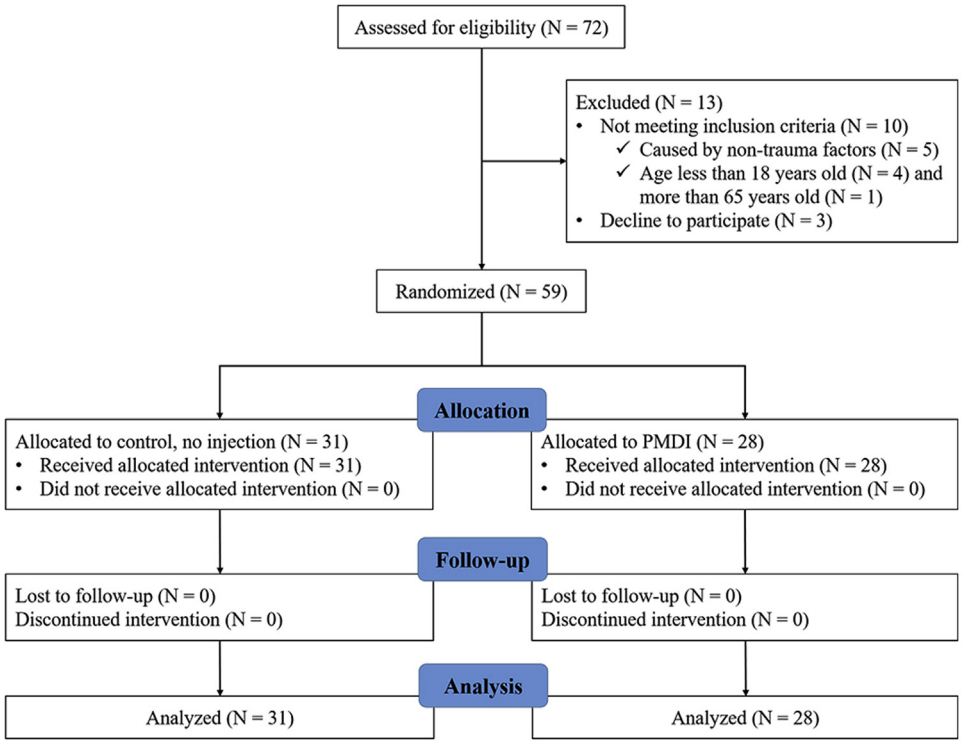

Figure 1 Consolidated Standards of Reporting Trials flowchart of the analysis. *PMDI*, periarticular multimodal drug injection.

the left end of the line and the patient's mark in mm. The VAS at rest was recorded 9 times: preoperatively, on OEA night, and on PODs 1-7. The VAS with motion was measured preoperatively and on PODs 1-7 during exercise. Additional parecoxib doses for rescue analgesia were recorded on OEA night, on PODs 1-3, and as the total dosage for the first postoperative week. Blood-loss volume through drains was recorded every 24 hours until drain removal on POD 3. ROM during rehabilitation was measured daily from day 1 to day 7 after surgery, as well as at 3-month follow-up.

We prospectively assessed complications with special attention to medication-related side effects, such as blurred vision, hearing problems, transient peripheral paralysis, dizziness, convulsion, muscle cramping or twitches, hypotension, bradycardia, and new-onset arrhythmia.

Sample size

We calculated that 26 patients per group would be required for this trial to detect a clinically relevant 20-mm mean decrease in the VAS score, given a 2-sided 5% significance level and 80% power. The 20-mm criterion was determined on the basis of previous literature on the efficacy of PMDI.[9,30] For power analysis, we used a standard deviation of 21 mm in the VAS score based on prior series of patients undergoing OEA.[31]

Statistical analysis

To analyze the primary outcome, we compared the mean differences (MD) and 95% confidence intervals (CIs) with results of the 2-tailed *t*-test. In addition, the MD in the primary outcome of pain was assessed to determine whether it met the minimum clinically important difference (MCID) of 20 mm as described above.

We used a 2-tailed *t*-test to analyze other continuous variables and a χ^2 test for categorical variables. Associated P values $<.05$ were considered statistically significant. Statistical analysis was performed with IBM SPSS version 24.0 (IBM, Armonk, NY, USA).

Results

Postoperative pain

The mean VAS score showed clinically important differences between the PMDI and control groups at rest on OEA night (MD, 25 mm; 95% CI: 18-31; $P < .001$) and with motion for the first 3 PODs (POD 1: MD, 28 mm, 95% CI: 21-34, $P < .001$; POD 2: MD, 21 mm, 95% CI: 13-30, $P < .001$; POD 3: MD, 21 mm, 95% CI: 14-29, $P < .001$). The elbows that received PMDI also had lower VAS pain scores at rest than the controls over the first 3 PODs (POD 1: MD, 16 mm, 95% CI: 11-21, $P < .001$; POD 2: MD, 10 mm, 95% CI: 3-18, $P = .008$; POD 3: MD, 6 mm, 95% CI: 1-12, $P = .017$); VAS was also different for the 2 groups on POD 4 (MD, 15 mm; 95% CI: 7-22; $P < .001$) and POD 5 (MD, 9 mm; 95% CI: 3-16; $P = .007$) with motion, but these differences did not reach the MCID level and so are unlikely to be clinically important. No significant

Table I Patient demographics and baseline clinical characteristics

Characteristics	PMDI (N = 28)	Control (N = 31)	MD/OR (95% CI)	*P* value
Age (yr)	39 ± 10	41 ± 13	1 (−5 to 8)	.650*
Male (n)	20 (71)	19 (61)	1.6 (0.5 to 4.7)	.411†
Height (cm)	171 ± 8	168 ± 9	−2 (−7 to 2)	.304*
Weight (kg)	70 ± 11	66 ± 11	−4 (−9 to 2)	.186*
Body mass index (kg/m^2)	24 ± 2	23 ± 3	−1 (−2 to 1)	.277*
Dominant arm (n)	16 (57)	22 (71)	0.5 (0.2 to 1.6)	.268†
Disease duration (mo)	22 ± 34	28 ± 33	6 (−11 to 24)	.473*
Initial injury (n)			1.2 (0.4 to 3.9)	.728†
Singular fracture	21 (75)	22 (71)		
Combined fractures	7 (25)	9 (29)		
Mechanism of injury (n)			1.1 (0.4 to 3.1)	.859†
Low energy	16 (57)	17 (55)		
High energy	12 (43)	14 (45)		
Preop VAS at rest (mm)	1 ± 5	2 ± 6	1 (−2 to 4)	.487*
Preop VAS on motion (mm)	6 ± 12	11 ± 15	5 (−2 to 12)	.171*
Preop ROM (°)	52 ± 29	44 ± 29	−7 (−23 to 8)	.333*
Surgical incision (n)			0.6 (0.2 to 1.8)	.393†
Combined lateral-medial	15 (54)	20 (65)		
Midline posterior	13 (46)	11 (35)		
Operative time (min)	151 ± 35	157 ± 64	6 (−22 to 33)	.676*
Intraoperative blood loss (mL)	113 ± 88	133 ± 73	20 (−22 to 63)	.339*
Tourniquet time (min)	58 ± 22	64 ± 32	5 (−9 to 20)	.477*
Intraoperative ROM recovery (°)	134 ± 6	133 ± 7	−1 (−4 to 3)	.627*

Preop, preoperative; *VAS*, visual analog scale; *ROM*, range of motion; *PMDI*, periarticular multimodal drug injection; *MD*, mean difference; *OR*, odds ratio; *CI*, confidence interval.

Fracture location was classified as singular (distal humerus, radial head, olecranon, or coronoid) or combined (concomitant fractures of the distal humerus, radial head, or proximal ulna involving >1 location); VAS score was rated using a 100-mm horizontal scale.

Categorical variables are presented as number (%); continuous variables are presented as mean ± standard deviation.

* *P* values were determined with the 2-tailed *t*-test.

† *P* values were determined with the $\chi 2$ test.

differences were found in the postoperative assessments at rest (POD 4, $P = .330$; POD 5, $P = .256$; POD 6, $P = .974$; POD 7, $P = .111$) or with motion (POD 6, $P = .088$; POD 7, $P = .196$) (Table II and Figs. 2 and 3).

Table III shows the numbers of additional parecoxib doses used as rescue analgesia, which was significantly lower in the PMDI group than in the control group on OEA night and on PODs 1-3. The PMDI group required lower total amounts of additional parecoxib consumption during the first postoperative week than the control group (MD, 148 mg; 95% CI: 77-219; $P < .001$).

Blood loss

Significantly lower blood-drainage volumes were found in the PMDI group than in the control group on POD 1 (132 ± 48 vs. 170 ± 68 mL; MD, 38; 95% CI: 7-68; $P = .016$) (Fig. 4), whereas no significant differences were found on POD 2 (110 ± 64 vs. 109 ± 66 mL; MD, −1; 95% CI: −35 to 33; $P = .950$) and POD 3 (56 ± 33 vs. 69 ± 49 mL; MD, 12; 95% CI: −9 to 34; $P = .259$) or in the total blood drainage (298 ± 114 vs. 347 ± 163 mL; MD, 50; 95% CI: −24 to 122; $P = .184$) (Fig. 5).

Postoperative ROM

The PMDI group exhibited a significantly better ROM during the first 4 PODs than the control group (POD 1: 119° ± 13° vs. 108° ± 17°, MD 11°, 95% CI: 3°-19°, $P = .007$; POD 2: 123° ± 11° vs. 114° ± 16°, MD 9°, 95% CI: 2°-16°, $P = .015$; POD 3: 129° ± 10° vs. 119° ± 14°, MD 10°, 95% CI: 4°-16°, $P = .002$; POD 4: 129° ± 9° vs. 122° ± 12°, MD 7°, 95% CI: 2°-13°, $P = .008$) (Fig. 6). At 3-month follow-up, no significant difference was found between the PMDI and control groups with respect to ROM (126° ± 12° vs. 122° ± 18°, MD 4°, 95% CI: 4°-12°, $P = .357$).

Complications

No medication-related side effects were recorded in the PMDI group, including pruritus, respiratory depression, blurred vision, hearing problems, transient peripheral paralysis, dizziness, delirium, convulsion, muscle twitch or cramp, hypotension, bradycardia, new-onset arrhythmia, or allergy to the medications.

Table II Comparison of postoperative pain levels between the periarticular multimodal drug injection (PMDI) and control groups

Time	At rest (VAS†)				On motion (VAS†)			
	PMDI (N = 28)	Control (N = 31)	MD (95% CI)	*P* value	PMDI (N = 28)	Control (N = 31)	MD (95% CI)	*P* value
POD 0‡	29 ± 15	53 ± 11	25 (18 to 31)	<.001*	–	–	–	–
POD 1	26 ± 11	42 ± 8	16 (11 to 21)	<.001*	45 ± 14	72 ± 10	28 (21 to 34)	<.001*
POD 2	23 ± 11	34 ± 18	10 (3 to 18)	.008*	41 ± 17	63 ± 13	21 (13 to 30)	<.001*
POD 3	22 ± 11	28 ± 9	6 (1 to 12)	.017*	38 ± 16	60 ± 12	21 (14 to 29)	<.001*
POD 4	25 ± 11	28 ± 10	3 (−3 to 8)	.330*	44 ± 12	59 ± 17	15 (7 to 22)	<.001*
POD 5	24 ± 9	27 ± 8	2 (−2 to 7)	.256*	43 ± 9	52 ± 16	9 (3 to 16)	.007*
POD 6	23 ± 10	23 ± 8	0 (−5 to 5)	.974*	42 ± 10	49 ± 19	7 (−1 to 15)	.088*
POD 7	18 ± 8	22 ± 10	4 (−1 to 9)	.111*	35 ± 11	40 ± 16	5 (−2 to 12)	.196*

POD, postoperative day; *VAS*, visual analog scale; *MD*, mean difference; *CI*, confidence interval.

* *P* values are determined with the 2-tailed *t*-test.

† VAS score was rated using a 100-mm horizontal scale, with a 20-mm difference representing the MCID; results are shown as means ± standard deviation.

‡ POD 0 is on the night of surgery.

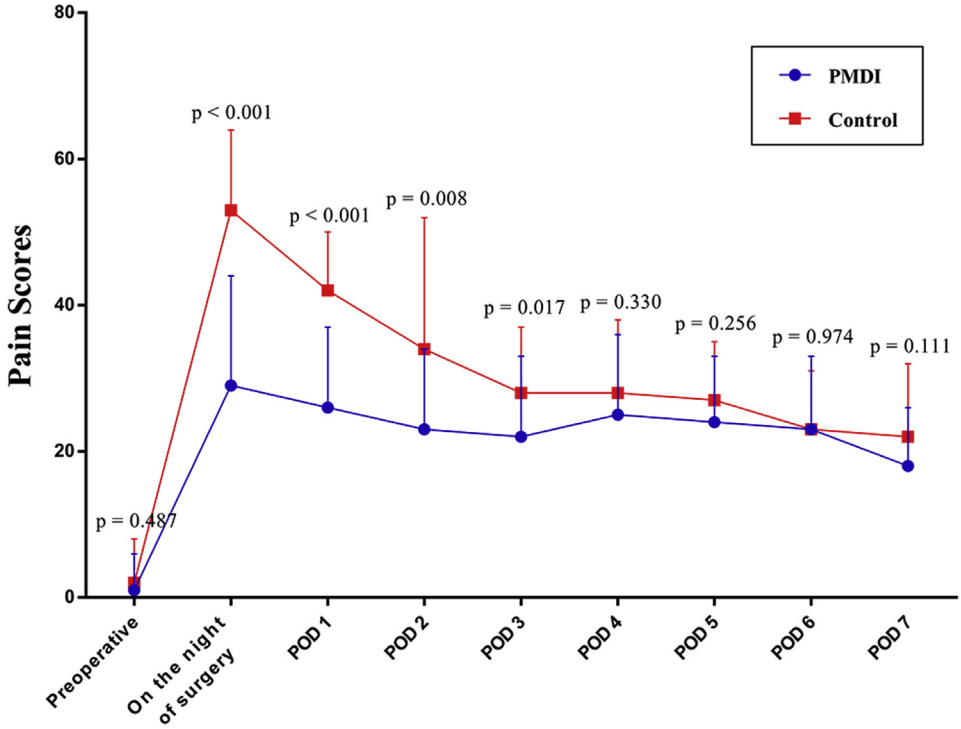

Figure 2 Visual analog scale scores for pain at rest after open elbow arthrolysis in patients receiving periarticular multimodal drug injection (PMDI) or no injections are shown. Clinically important differences could be seen between the PMDI and control groups on the night of surgery (29 ± 15 vs. 53 ± 11 mm; $P < .001$). The elbows that received PMDI also had lower scores than the controls over the first 3 postoperative days (PODs) (POD 1: mean difference [MD] 16 mm, $P < .001$; POD 2: MD 10 mm, $P = .008$; POD 3: MD 6 mm, $P = .017$), but these differences did not reach the level of the minimum clinically important difference. No significant differences were found in the rest postoperative assessments.

Discussion

To the best of our knowledge, this was the first study of PMDI application in OEA. Ultimately, we found that PMDI is effective on relieving pain and reducing analgesic consumption after OEA with no apparent increase in risk, helping facilitate postoperative rehabilitation.

We used ropivacaine, epinephrine, and ketorolac as active ingredients of the infiltration mixture. Ropivacaine is pharmokinetically similar to bupivacaine, but it is longer-acting and associated with less cardiac and central nervous system toxicity, allowing one to tolerate a larger dose.[4] The reported maximum concentration of venous ropivacaine observed in the PMDI group was 60 ng/mL, 2.5 times

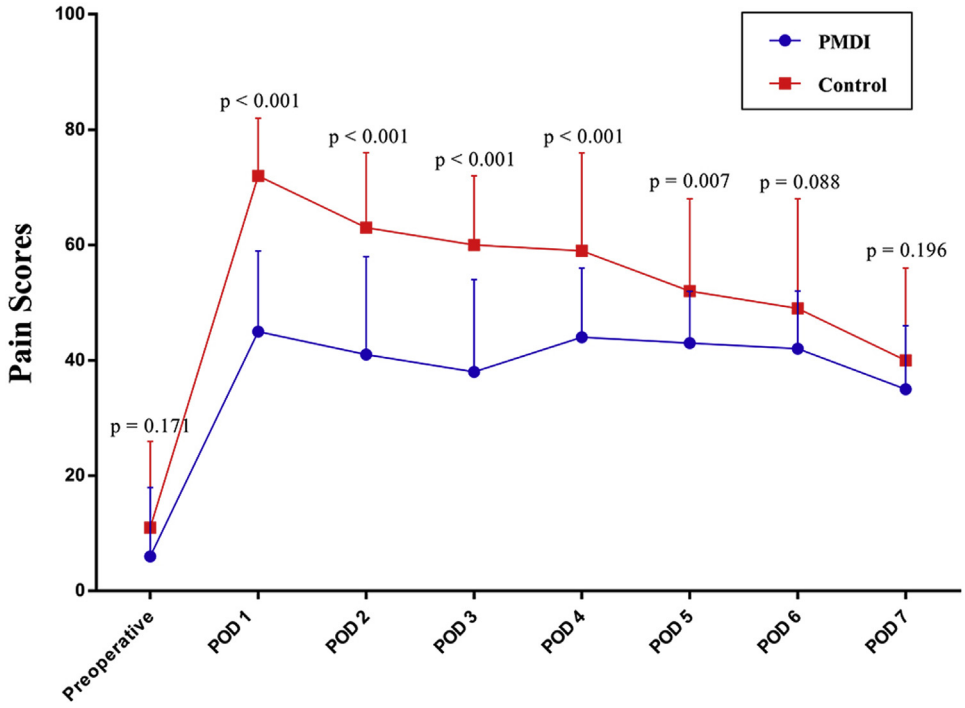

Figure 3 Visual analog scale scores for pain with motion after open elbow arthrolysis in patients receiving periarticular multimodal drug injection (PMDI) or no injections are shown. Clinically important differences could be seen between the PMDI and control groups for the first 3 postoperative days (PODs) (POD 1: 45 ± 14 vs. 72 ± 10 mm, $P < .001$; POD 2: 41 ± 17 vs. 63 ± 13 mm, $P < .001$; POD 3: 38 ± 16 vs. 60 ± 12 mm, $P < .001$). The elbows that received PMDI also had lower scores than the controls on POD 4 (mean difference [MD], 15 mm; $P < .001$) and POD 5 (MD, 9 mm; $P = .007$), but these differences did not reach the level of the minimum clinically important difference. No significant differences were found in the rest postoperative assessments.

Table III The use of rescue analgesia

Time	PMDI[†] (N = 28)	Control[†] (N = 31)	MD (95% CI)	*P* value
On the night of surgery	3 ± 10	22 ± 20	19 (11-27)	<.001[*]
Postop day 1	14 ± 22	55 ± 30	41 (27-55)	<.001[*]
Postop day 2	13 ± 22	34 ± 33	21 (6-35)	.006[*]
Postop day 3	7 ± 19	26 ± 35	19 (4-33)	.013[*]
Total[‡]	40 ± 71	188 ± 180	148 (77-219)	<.001[*]

Postop, postoperative; *PMDI*, periarticular multimodal drug injection; *MD*, mean difference; *CI*, confidence interval.

[*] *P* values are determined with the 2-tailed *t*-test.

[†] The values are expressed as the mean number of additional parecoxib consumption (mg) used as rescue analgesia and the standard deviation.

[‡] The total amounts are the sum of additional parecoxib consumption used as rescue analgesia during the first postoperative week.

below the toxic levels (150 ng/mL).[12] Epinephrine helps reduce the toxicity of local anesthetic by keeping it localized to the injection area and helps release into the vascular system and prolong its local action.[23] The NSAID (ketorolac) in the multimodal analgesic regimen reduces peripheral sensitization and activation of nociceptors by inhibiting the eicosanoid pathway that leads to production of inflammatory mediators[16] and is approved for enhancement of soft-tissue healing and prevention of heterotopic ossification.[6,24] Some centers sometimes add an opioid (epimorphine) into the mixture.[11] However, the efficacy and safety of periarticular opioid injection is still controversial and needs further research.[10]

In this study, the PMDI group had statistically significantly lower VAS pain scores, both at rest and motion, and less additional parecoxib consumption on OEA night and during the first 3 PODs. Because this was the first report of PMDI in OEA, we compared the results with reports in TKA, a more common orthopedic surgery worldwide. Although the stated efficacy of this intervention is not consistent across different studies (some RCTs compared PMDI with no or placebo injection, with varying

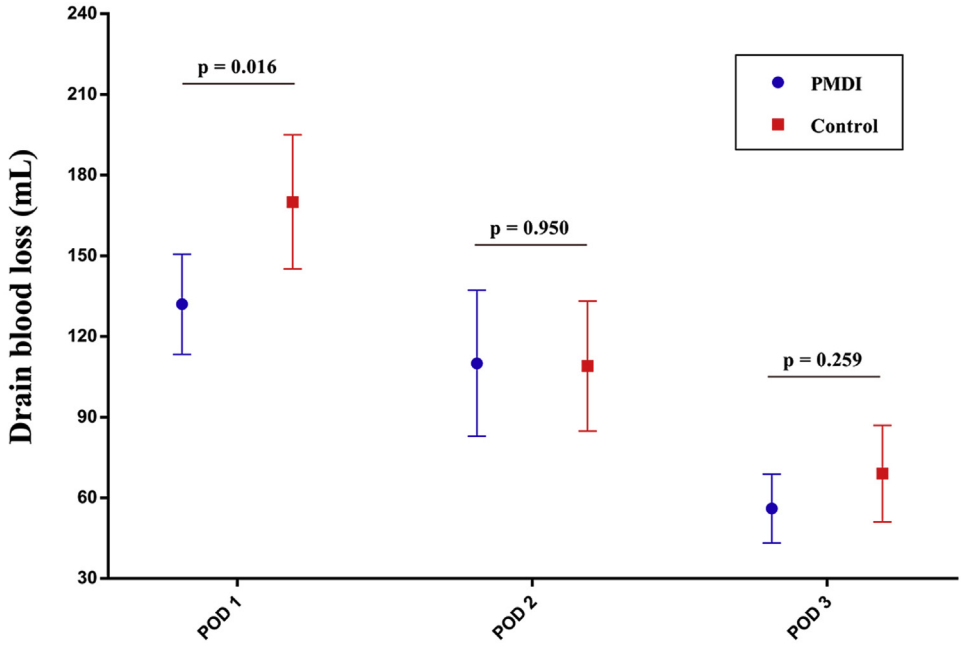

Figure 4 Drain blood loss during the first 3 postoperative days (PODs) after open elbow arthrolysis in patients receiving periarticular multimodal drug injection (PMDI) or no injections is shown. Significantly lower blood-drainage volumes were found in the PMDI group compared with the control group on POD 1 (132 ± 48 vs. 170 ± 68 mL; $P = .016$), whereas no significant differences were found on POD 2 (110 ± 64 vs. 109 ± 66 mL; $P = .950$) and POD 3 (56 ± 33 vs. 69 ± 49 mL; $P = .259$).

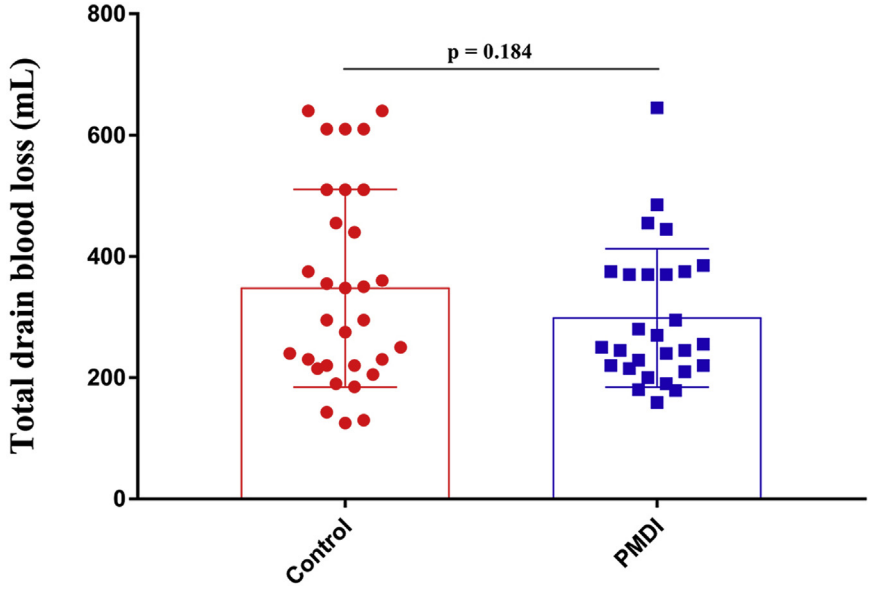

Figure 5 Total drain blood loss after open elbow arthrolysis in patients receiving periarticular multimodal drug injection (PMDI) or no injections is shown. No significant difference was found in the 2 groups (298 ± 114 vs. 347 ± 163 mL; $P = .184$).

conclusions; other RCTs compared PMDI with other pain-relief regimens, again with varying results), the trend from a meta-analysis of 16 RCTs with 1447 TKAs showed that PMDI yielded lower VAS for 6, 24, and 48 hours at rest and with motion, and less analgesic consumption at 24 and 48 hours postoperatively.[11] Our results compare favorably with those reports, implying that PMDI should have similar efficacy and produces better pain relief and less drug consumption as effectively after OEA as after TKA.

However, statistical differences are not what patients seek; clinical decisions should be made whether differences are below or above the MCID.[19] Recently, Hirasawa[9] performed an RCT among patients who underwent THA between PMDI and placebo, and found that the PMDI group

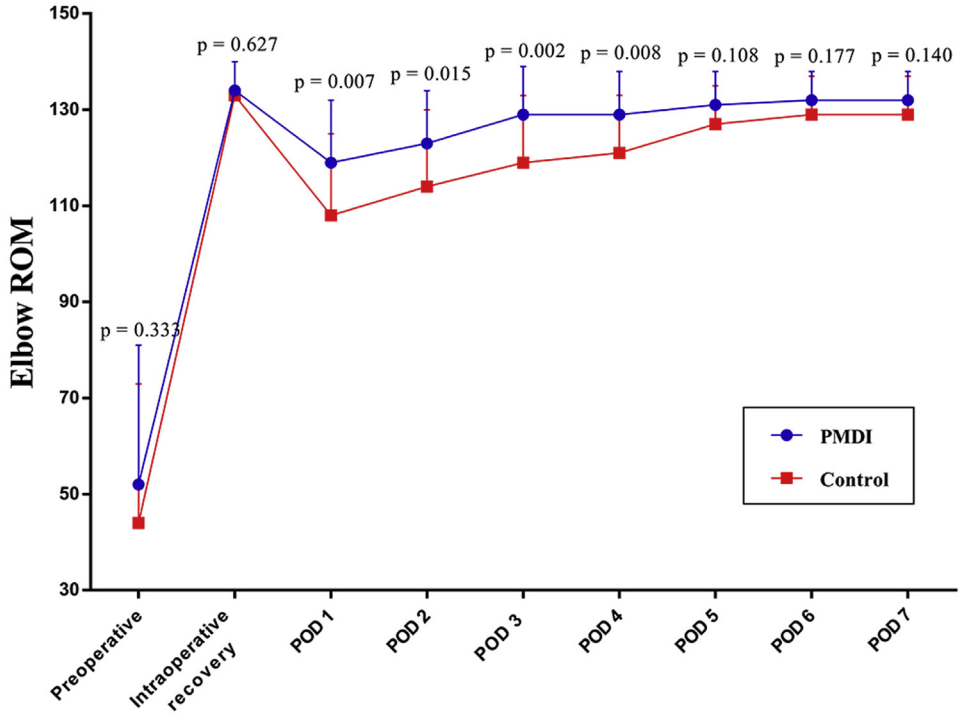

Figure 6 Elbow range of motion (ROM) during rehabilitation after open elbow arthrolysis in patients receiving periarticular multimodal drug injection (PMDI) or no injections is shown. Significantly better ROM was seen in the PMDI group during the first 4 postoperative days (PODs) (POD 1: 119° ± 13° vs. 108° ± 17°, $P = .007$; POD 2: 123° ± 11° vs. 114° ± 16°, $P = .015$; POD 3: 129° ± 10° vs. 119° ± 14°, $P = .002$; POD 4: 129° ± 9° vs. 122° ± 12°, $P = .008$). No significant differences were found in postoperative assessments at rest.

had less pain than those receiving placebo at 3 time points, in the recovery room (MD, 14 mm; $P = .004$), 3 hours postoperatively (MD, 9 mm; $P = .010$), and 24 hours postoperatively (MD, 6 mm; $P = .006$). However, none exceeded the MCID (20 mm) and thus were unlikely to be clinically important. To our knowledge, MCID has not been previously established for the VAS pain score after OEA. Provisionally, we also used the 20-mm mean decrease as the MCID based on previous reports investigating the efficacy of PMDI.[9,30] In our study, the mean VAS showed clinically important differences between PMDI and control groups at rest on OEA night and the first 3 PODs with motion, but not in the remaining postoperative assessments. The VAS was found to decline progressively from OEA night to POD 3 both at rest and with motion in both PMDI and control groups; however, a slight rise was detected from POD 3 to POD 4 in the PMDI group, but not in the control group. We believe that this interesting finding suggests that PMDI has an approximate effective period of 3 PODs after OEA.

In this study, significantly less blood drainage was found in the PMDI group vs. the control group on POD 1, but not on POD 2 or POD 3 or in total. The effect of PMDI on blood loss reduction is believed to be a direct result of epinephrine causing vasoconstriction, its platelet-stimulating effect through α2 adrenoreceptors, and tumescent effect of a large bolus's infiltration into local soft tissues.[32] A statistically significant reduction in blood loss of 371 mL was found in patients undergoing TKA with PMDI compared with the placebo group,[18] whereas other studies showed negative results.[18,21] The efficacy of norepinephrine is isolated to the blood flow peak that is normally present for 20-30 minutes after tourniquet release.[15] The local infusion of norepinephrine before releasing the tourniquet induces contraction of peripheral vessels, reducing this peak. We believe that this phenomenon, and postoperative rehabilitation beginning on POD 1, might explain why the PMDI group had less blood drainage on POD 1 but not on PODs 2 and 3 or total.

In this study, the PMDI group exhibited a significantly better ROM during rehabilitation on the first 4 PODs. Functional recovery was also an important issue relating pain management after surgery to early postoperative mobilization. The same meta-analysis cited above showed that PMDI yielded greater knee ROM on POD 1 (MD, 13°; 95% CI: 8-19), POD 2 (MD, 12°; 95% CI: 8-17), and POD 3 (MD, 11°; 95% CI: 8-14).[11] Our results compare favorably with those reports, which may be explained by the pain scores in the current study being consistently lower, with clinically important differences in the PMDI group, on the first 3 PODs during rehabilitation. In addition, the control group gained no more amplitudes compared with the PMDI group, which could reduce the potential bias, while not existed now, that the more painful during rehabilitation in the control group would be attributed to their more ROM.

There were no complications attributable to the injections during this study period. Although no previous studies have shown that PMDI substantially influences complications except for postoperative nausea, more serious side effects like allergies may occur. Our study was underpowered to analyze the influence of PMDI on complications. A systematic review containing 10 RCTs with 1216 TKAs showed no differences (within 2 weeks) in wound complications and deep vein thrombosis, but a significant reduction in the rate of nausea or vomiting, and rash or pruritus.[29]

We acknowledge several limitations. First, as no standard formula of drug cocktail has been reported in elbow-related surgeries, the example from Mayo Clinic for TKA was used.[1] However, we are unsure whether this is the optimal mixture or drug concentration for elbow surgeries. Second, rescue analgesia could mask the effectiveness of PMDI, although we believed that this effect would be small because the mean number of rescue analgesia doses was relatively low. Third, only drain output was used to define blood loss, which would fail to recognize the hidden blood loss into soft tissues.[7,20] Fourth, MCID of 20 mm in VAS was generated from patients undergoing TKA and THA, which was not clear in the specific population of PTES up till now, and could be delivered in future study. Fifth, we did not have a more typical control group like peripheral nerve block, either a single shot or a continuous regional block, which would make the results more meaningful. Sixth, a randomized method like computerized variable allocation may be better than an opaque envelope, with less additional supervision, operative time, and bias. Seventh, the small sample size, although adequate to establish clinical outcome differences, combined with the exclusion criteria like nontraumatic stiffness and age range, might make the results to be underpowered to evaluate for complications, limit the evaluation in the risk of uncommon complications, and increase bias for the efficacy.

Conclusion

PMDI is effective in relieving pain and reducing analgesic consumption after OEA. It presents no apparent increase in risk and helps facilitate postoperative rehabilitation. Further prospective research with larger populations, at multiple clinical centers, using other mixtures and/or concentrations of drugs, and/or comparing PMDI with other analgesia regimens, is needed.

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