

Intravenous versus Ultrasound Guided Thoracic Paravertebral Morphine-Dexmedetomidine Combination in Patients with Multiple Rib Fractures

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Abstract

Background: Severe pain caused by multiple rib fractures (MRF) can compromise oxygenation, ventilation and pulmonary functions so can affect patient outcome. Adequate pain control helps to avoid these complications. Thoracic paravertebral analgesia is comparable to thoracic epidural with fewer side effects.

Methods: Seventy-five patients were randomly allocated into three groups, (n=25 each). Group (G_M) received intravenous morphine with a loading dose of 0.1-0.2 mg/kg followed by PCA bolus of 1mg with a six min lockout. Group (G_{MD}) received also intravenous morphine with a loading dose of 0.1-0.2 mg/kg then PCA bolus of 1 mg morphine plus 5 µg dexmedetomidine with a six min lockout. Group (G_{PV}) received paravertebral morphine loading dose of 0.2 mg/kg then PCA bolus of 0.1 ml/kg of a solution with a concentration of 0.5 mg/ml morphine mixed with 1 µg/ml dexmedetomidine and 60 min lockout. Any patient with VAS score more than 4, a top-up dose was given until VAS ≤ 4

Results: No significant difference between the three groups as regards age, BMI, sex, and ASA. Road traffic accident was the main cause of blunt chest trauma (64%, 76% and 68% in G_M, G_{MD}, and G_{PV} respectively). Total morphine requirements were significantly lower in G_{MD} and G_{PV} than G_M and in G_{PV} than G_{MD} (G_M=190.9 ± 45.26, G_{MD}=117.1 ± 31.9 and G_{PV}=86.2 ± 21.7). There was a significant decrease in nausea and vomiting in G_{MD} and G_{PV} than G_M. No significant difference in RR between the three groups although 8 patients in GM developed respiratory depression which was significantly higher than in G_{MD} (2 patients) and G_{PV} (0 patient). No significant difference in HR, MAP, and SpO₂ between the groups. VAS scores at rest and with cough were significantly lower in both G_{MD} and G_{PV} than G_M. FVC, FEV1 and PaO₂/FiO₂ ratio were significantly increased and PaCO₂ significantly decrease in G_{MD} and G_{PV} than G_M.

Conclusion: Adding dexmedetomidine to morphine either TPV or IV PCA significantly decreases VAS scores, improves pulmonary functions and also decrease morphine consumption with fewer side effects in patients with MRF.

Keywords: Thoracic paravertebral block; Patient controlled analgesia; Dexmedetomidine; Morphine; Multiple rib fractures

Introduction

Pain caused by fracture of one or two ribs is usually controlled efficiently by oral analgesic drugs [1]. However pain accompanying multiple rib fractures (three ribs or more) can be severe and may limit the ability to breathe and cough. Retention of secretions increase the risk of pulmonary infection, atelectasis and affection of respiratory mechanics can take place and may result in respiratory failure [2-4]. Systemic opioids are often the first-line for pain control in patients with MRF however their use can result in over-sedation, respiratory depression and cough suppression and so patients become unable to cough and expectorate effectively [2]. Because of that, regional anesthetic techniques are preferred for managing such patients as intercostal nerve block (ICNB), epidural analgesia, and thoracic paravertebral block (TPVB) and intrapleural analgesia [5]. Epidural analgesia is considered the best pain control modality for severe pain with MRF but it has some complications such as hypotension, bradycardia and bilateral block than TPVB that has a comparable

analgesic effect to thoracic epidural analgesia [6-8]. Patient-controlled analgesia is recently considered in some trials. It allows the patient to deliver his own analgesic and it is rarely dispensing a wrong medication dose if it is programmed and operates as intended [9]. Dexmedetomidine, a medetomidine's dextrogyrous enantiomer [10], possess an opioid-sparing effect due to its high selective α₂ adrenoceptor agonist effect [11]. It has been recently proved that perioperative dexmedetomidine administration reduces postoperative morphine requirements even without loading dose [12-16]. Dexmedetomidine has a synergistic action with opioids [17]. The aim of this study was to evaluate the effects of morphine-dexmedetomidine combination either intravenous or paravertebral in chest trauma patients with unilateral MRF.

Patients and Methods

After approval of hospital ethical committee and obtaining a written, informed consent, 75 patients between the age of 20 and 50 years old with unilateral MRF were included in our study. The pain control regimen used in this study was explained for all the patients and the Visual Analogue Score (VAS) was taught to them to know how

to rate their pain severity scored from 0 to 10; while 0 stands for no pain at all and 10 is the worst intolerable pain. Also, patients were educated for PCA.

Patients with unilateral MFR (3 or more ribs), hemodynamically stable, fully conscious and hemothorax or pneumothorax had been drained were included in this study. Patients who required any surgical intervention had been done before starting the study. We excluded patients with mechanical ventilation, disturbed conscious level, severe traumatic spinal cord or brain injury, spinal fracture or deformity, renal or hepatic diseases, anticoagulation and previously known allergy to study drugs or infection at the site of needle insertion. Patients who refuse to continue the analgesic modality and those who became sedated, intubated or mentally disturbed after starting the study were also excluded.

For each patient, IV access line and arterial line was secured and standard monitoring including ECG, SpO₂ and invasive arterial blood pressure were applied. With the patient in the sitting position and under complete aseptic technique, the paravertebral space two segments below the upper most fractured rib or midway between the uppermost and the lowest fractured rib was identified by using real-time ultrasound guidance, ultrasound machine (sonoscape[®] SSI-6000) and A 12 MHz linear type probe. After local infiltration of the skin and underlying tissues by using 3 ml of 1% lidocaine solution, an 18 gauge Touhy needle (B.Braun, Perifix, Germany) was used to thread an epidural catheter that is advanced 3-4 cm into the paravertebral space then the needle was removed and the catheter was tunneled subcutaneously and fixed to the back of the patient. The patient then positioned supine and 3 ml of lidocaine 2% with 5 µg/ml epinephrine was injected as a test dose after negative aspiration of blood or CSF.

Patients were allocated randomly into one of three groups, 25 patients each, using a computer-generated random number assignment in sealed envelopes. Group (G_M) received intravenous morphine with initial loading dose of 0.1-0.2 mg/kg and once adequate analgesia attained, PCA started using a bolus of 1 mg with lockout period of six min. Group (G_{MD}) received also intravenous morphine with initial loading dose of 0.1-0.2 mg/kg and once adequate analgesia attained, PCA started using bolus of 1 mg morphine plus 5 µg dexmedetomidine with a lockout period of six min. For G_M, The solution prepared in a 50 ml syringe with morphine concentration of 1 mg/ml and for G_{MD}, dexmedetomidine 5 µg/ml is added. Group (G_{PV}) received paravertebral loading morphine dose of 0.2 mg/kg then a solution in a 50 ml syringe was prepared with a concentration of 0.5 mg/ml morphine mixed with 1 µg/ml dexmedetomidine and bolus of 0.1 ml/kg by PCA machine and lock out period of 60 min. PCA machines were programmed without background continuous infusion. If any patient still has VAS scores >4, a top-up dose of the prepared solution given till VAS scores of 4 or less. Patients who developed hypotension (20% less than the initial MAP), first received 500 ml of normal saline and if persistent, IV ephedrine 5-10 mg bolus was given and could be repeated. Bradycardia (HR ≤ 50 beat/min) was treated with IV atropine 0.5 mg.

Measurements

HR, mean arterial blood pressure (MAP), respiratory rate (RR), arterial oxygen saturation (SpO₂), and VAS scores at rest and with cough were recorded at baseline just before starting any medication. HR and MAP were measured every 5 min for the first 15 min. After that all parameters-HR, MAP, RR, SpO₂, and VAS scores at rest and with cough-reassessed and recorded at 30 min, 1 h, 2 h, 4 h, 8 h, 12 h

and then every 6 h until 48 h (the study period). FEV1, FVC (using a portable spirometer; FlowScreens, Erich Jaeger, Wurzburg, Germany), PaO₂/FiO₂ ratio and PaCO₂ through arterial blood gas analysis were recorded at baseline and then every 8 h until 48 h. Total morphine requirement during the study period (48 h) was also recorded. At the end of the study period (48 h), all patients were questioned about the effectiveness of pain control regimen and asked to rate their satisfaction of the analgesia achieved as optimum, adequate or inadequate.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0, IBM, Armonk, NY, United States of America. Quantitative data expressed as mean values ± standard deviation (SD) and interquartile range (IQR) and median. Qualitative data expressed as frequency and percentage. A one-way analysis of variance (ANOVA) was used when comparing between more than two means, Post Hoc test for multiple comparisons between different variables, Kruskal-Wallis test when comparing between more than two median in non-parametric data, Mann-Whitney U-test when multiple comparisons between different variables in non-parametric data and Chi-square (X²) test of significance was used to compare proportions between two qualitative parameters. P value of less than 0.05 was considered significant*. P1, P2, P3 represented the comparison between G_M and G_{MD}, G_M and G_{PV} and G_{MD} and G_{PV} respectively.

Results

There were no significant difference between the three groups as regards the demographic data including age, BMI, sex and ASA classification of the patients. Road traffic accident were the main cause of blunt chest trauma in the three groups (64%, 76% and 68% in GM, GMD and GPV respectively) but there were some cases due to falling from height or direct trauma and there were no significant difference between the groups when the causes of MFRs were compared (Table 1).

Total morphine requirements during the study period (48 h) was significantly lower in G_{MD} and G_{PV} than G_M (G_M=190.9 ± 45.26, G_{MD}=117.1 ± 31.9 and G_{PV}=86.2 ± 21.7). Also morphine requirements were significantly lower in GPV than GMD. This reduction in morphine consumption results in significant decrease in morphine associated side effects as nausea and vomiting in GMD and GPV than GM however no significant difference between the groups as regards itching (Table 2).

There was no significant difference in RR between the three groups although 8 patients in G_M developed respiratory depression throughout the study period which was significantly higher than in G_{MD} (2 patients) and G_{PV} (0 patient) but no patient required intubation and mechanical ventilation (Table 2).

Regarding HR and MBP, there were no significant differences between the three groups throughout the study period. Patients who experienced bradycardia and/or hypotension (Table 3) did not require pharmacological interference except one patient in GMD who received IV 0.5 mg atropine and only IV infusion of 500 ml normal saline was enough to manage patients who had hypotension. Also, there was an insignificant difference between the three groups in terms of SpO₂. VAS scores at rest and with cough were significantly lower in both G_{MD} and G_{PV} than G_M. However, when comparing VAS scores at rest

and with cough between G_{MD} and G_{PV} , there was no significant difference (Figures 1 and 2).

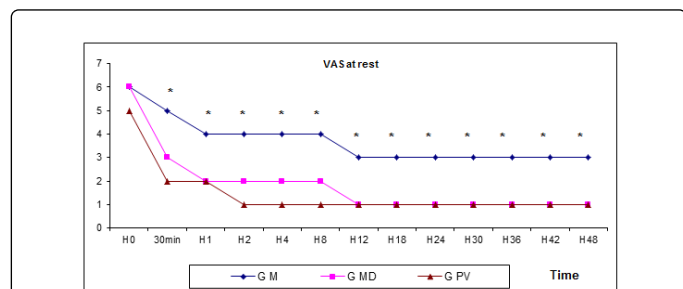


Figure 1: Comparison of VAS at rest between the three groups.

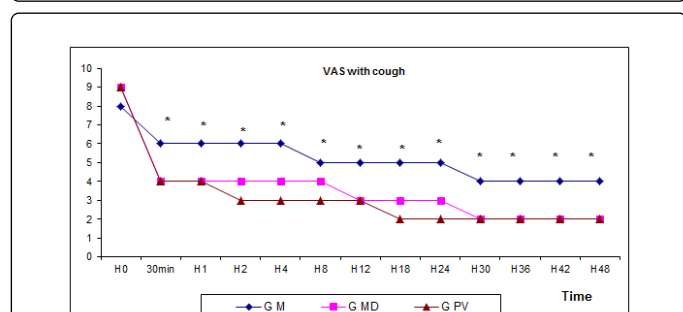


Figure 2: Comparison of VAS with cough between the three groups.

FVC and FEV1 were significantly increased in G_{MD} and G_{PV} than G_M ; however, there was an insignificant difference when comparing G_{MD} and G_{PV} (Figures 3 and 4).

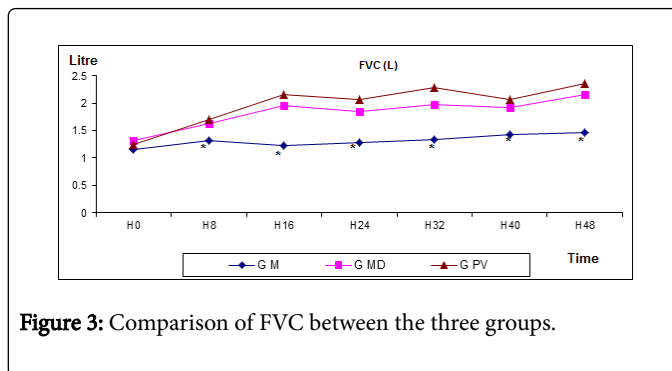


Figure 3: Comparison of FVC between the three groups.

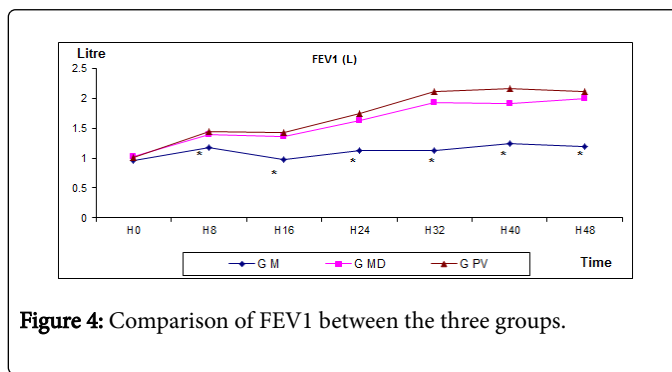


Figure 4: Comparison of FEV1 between the three groups.

Regarding PaO_2/FiO_2 ratio and $PaCO_2$, there was a significant increase in PaO_2/FiO_2 ratio and a significant decrease in $PaCO_2$ in G_{MD} and G_{PV} than G_M , however, there was no significant difference between G_{MD} and G_{PV} in terms of PaO_2/FiO_2 ratio and $PaCO_2$ (Tables 4 and 5). Most of the patients in G_{PV} (84%) were optimally satisfied with the quality of analgesia and pain control technique and this was significantly higher than in G_{MD} (24%) and G_M (8%) (Table 6).

		G_M (n=25)	G_{MD} (n=25)	G_{PV} (n=25)	p. value
Age	Mean \pm SD	34.97 \pm 11.53	36.38 \pm 10.48	37.14 \pm 11.96	0.568
BMI	Mean \pm SD	31.52 \pm 9.18	29.94 \pm 8.79	32.18 \pm 9.78	0.462
Sex	Male (%)	20 (80%)	21 (84%)	23 (92%)	0.709
	Female (%)	5 (20%)	4 (16%)	2 (8%)	
ASA	I	10 (40%)	8 (32%)	11 (44%)	0.881
	II	9 (36%)	11 (44%)	10 (40%)	
	III	6 (24%)	6 (24%)	4 (16%)	
Cause of MFRs	RTA	16 (64%)	19 (76%)	17 (68%)	0.881
	Falling from height	6 (24%)	2 (8%)	4 (16%)	
	Direct trauma	3 (12%)	4 (16%)	4 (16%)	

BMI: Body Mass Index; ASA: American Society of Anesthesiologists; RTA: Road Traffic Accident.

Table 1: Demographic data and causes of multiple fracture ribs among the three groups.

Side effect	G_M (n=25)	G_{MD} (n=25)	G_{PV} (n=25)	p. value	P1	P2	P3
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Total morphine requirements in 48 h (mg)	190.9 ± 45.26	117.1 ± 31.9	86.2 ± 21.7	0.001*	0.001*	0.001*	0.001*
Nausea	11 (44%)	4 (16%)	1 (4%)	0.002*	0.031*	0.001*	0.082
Vomiting	6 (24%)	1 (4%)	0 (0%)	0.022*	0.008*	0.009*	0.312
Itching	5 (20%)	2 (8%)	2 (8%)	0.321	-	-	-
Respiratory depression (RR ≤ 8)	8 (32%)	2 (8%)	0 (0%)	0.002*	0.034*	0.004*	0.149

Table 2: Total morphine requirements and side effects between the three groups.

Variable	G _M (n=25)	G _{MD} (n=25)	G _{PV} (n=25)	p. value
Bradycardia	1 (4%)	3 (12%)	2 (8%)	0.581
Hypotension	2 (8%)	4 (12%)	2 (8%)	0.571

Table 3: Bradycardia and hypotension in the three groups.

Time and Groups		Mean ± S. D	F. test	p. value	Post Hoc test	
H0	G _M	170.8 ± 22.3	2.045	0.254	P1	0.197
	G _{MD}	175.3 ± 23.5			P2	0.874
	G _{PV}	169.9 ± 21.8			P3	0.128
H8	G _M	138.2 ± 25.6	4.523	0.008*	P1	0.012*
	G _{MD}	175.5 ± 24.8			P2	0.001*
	G _{PV}	186.9 ± 27.3			P3	0.124
H16	G _M	149.9 ± 28.9	4.987	0.006*	P1	0.017*
	G _{MD}	171.4 ± 27.9			P2	0.001*
	G _{PV}	185.49 ± 26.7			P3	0.136
H24	G _M	132.9 ± 21.9	5.327	0.001*	P1	0.008*
	G _{MD}	174.5 ± 34.5			P2	0.001*
	G _{PV}	184.6 ± 36.6			P3	0.096
H32	G _M	140.1 ± 24.9	6.214	0.001*	P1	0.005*
	G _{MD}	164.5 ± 26.9			P2	0.001*
	G _{PV}	172.9 ± 31.6			P3	0.109
H40	G _M	145.9 ± 21.8	5.986	0.001*	P1	0.007*
	G _{MD}	178.7 ± 22.5			P2	0.001*
	G _{PV}	189.5 ± 29.6			P3	0.119
H48	G _M	134.6 ± 26.9	6.267	0.001*	P1	0.003*
	G _{MD}	175.9 ± 34.6			P2	0.001*
	G _{PV}	185.7 ± 39.5			P3	0.097

Table 4: Comparing changes in PaO₂/FiO₂ ratio between the three groups.

Time and Groups		Mean ± S. D	F. test	p. value	Post Hoc test	
H0	G _M	44.18 ± 5.34	0.318	0.642	P1	0.574
	G _{MD}	43.73 ± 5.19			P2	0.849
	G _{PV}	45.45 ± 4.97			P3	0.457
H8	G _M	45.81 ± 5.92	6.754	0.001*	P1	0.006*
	G _{MD}	40.78 ± 4.57			P2	0.001*
	G _{PV}	41.92 ± 4.89			P3	0.429
H16	G _M	45.65 ± 4.86	5.947	0.001*	P1	0.005*
	G _{MD}	41.17 ± 4.52			P2	0.001*
	G _{PV}	39.65 ± 3.78			P3	0.246
H24	G _M	46.71 ± 5.69	6.125	0.001*	P1	0.002*
	G _{MD}	40.57 ± 5.78			P2	0.001*
	G _{PV}	40.08 ± 4.76			P3	0.658
H32	G _M	44.83 ± 4.09	6.358	0.001*	P1	0.003*
	G _{MD}	39.98 ± 5.03			P2	0.001*
	G _{PV}	39.13 ± 5.12			P3	0.528
H40	G _M	46.17 ± 5.63	6.874	0.001*	P1	0.004*
	G _{MD}	41.09 ± 5.84			P2	0.001*
	G _{PV}	40.91 ± 5.61			P3	0.351
H48	G _M	47.93 ± 5.99	7.324	0.001*	P1	0.004*
	G _{MD}	40.78 ± 6.02			P2	0.001*
	G _{PV}	39.82 ± 4.74			P3	0.291

Table 5: Comparing changes in PaCO₂ between the three groups.

Satisfaction	GM (n=25)	GMD (n=25)	GPV (n=25)	p. value	P1	P2	P3
Optimum	2 (8%)	6 (24%)	21 (84%)	0.001*	0.123	0.001*	0.001*
Adequate	7 (28%)	17 (68%)	4 (16%)	0.001*	0.005*	0.306	0.001*
Non adequate	16 (64%)	2 (8%)	0 (0%)	0.001*	0.001*	0.001*	0.149

Table 6: Comparing Patient analgesia satisfaction between the three groups.

Discussion

Severe torturous pain caused by MRF is a clinical challenge that may result in serious respiratory complications with an increased risk of morbidity and mortality [5,16]. Management of these patients is mainly dependent on urgent and adequate pain control to help them breathe and cough effectively and cooperate for chest physiotherapy in order to maintain normal ventilation [16-18]. Dexmedetomidine has analgesic effect mediated through its action at the level of brain and brain stem, spinal cord and also at peripheral tissues [19] which is not dose-dependent; however, its hemodynamic associated effects are dependent on its dose [20,21].

Our results demonstrated that adding dexmedetomidine to intravenous morphine reduced morphine consumption by approximately 39% and when this combination used for TPVB, morphine consumption reduced more by about 26%. So it's of great importance to consider paravertebral morphine-dexmedetomidine mixture to manage pain in patients with MRF to avoid the deleterious side effects of a morphine overdose in such patients. To our knowledge, no other study had investigated the combination of dexmedetomidine and morphine for TPVB or IV PCA in patients with MRF.

The results of our study showed significantly lower VAS scores at all-time intervals at rest and with cough in G_{MD} and G_{PV} than in G_M and

no significant difference between G_{MD} and G_{PV} ; however, we found significantly lower morphine consumption in G_{PV} than in G_{MD} and G_M . Also, the current study revealed a significantly lower incidence of nausea, vomiting and respiratory depression in G_{PV} and G_{MD} than in G_M which can be explained by lower morphine consumption. Moreover, better patient analgesia satisfaction in G_{PV} than in G_M and G_{MD} .

Our results correlate with T.F Lin et al.; they investigated 100 patients to study the effects of adding dexmedetomidine to morphine for intravenous PCA and its associated side effects. They concluded that dexmedetomidine is a good adjuvant to morphine that can reduce morphine requirements together with better analgesic quality, higher patient satisfaction and lower incidence of nausea and vomiting in patients received morphine-dexmedetomidine mixture [22].

Iman Ghandi et al. who compared IV morphine with IV dexmedetomidine for pain control after open heart surgery concluded that dexmedetomidine ensures better analgesia with fewer side effects as respiratory depression, atelectasis, nausea, itching, intubation time and intravenous morphine consumption [23]. Also, Mohta et al. and Sinha et al. concluded that adding dexmedetomidine to paravertebral bupivacaine results in better analgesia and lower VAS scores [24,25].

Our results correlate with that of Ahmed R.Morsy et al. who compared dexmedetomidine versus morphine as an adjuvant for bupivacaine in paravertebral block for perioperative analgesia and concluded that adding dexmedetomidine to bupivacaine significantly reduced the postoperative pain, lower postoperative analgesic requirements and increase the time to first analgesic request but they are in disagreement with us as they reported significant reduction in MAP and HR in dexmedetomidine group and this can be explained by the use of high dose dexmedetomidine (100 μ g) [26].

Our results also revealed another fascinating point that adding dexmedetomidine to morphine either IV or paravertebral without dexmedetomidine loading dose helped to avoid the annoying side effect of dexmedetomidine in form of accompanying hypotension and bradycardia [16,21], especially in trauma patients as in our study. This was obvious in our results when analyzed as we found comparable MAP and HR between the three groups throughout the study period with no significant differences.

Our study results were in correspondence with that of Al-Mostafa et al. [27] and Gupta et al. [28] as they concluded that no hemodynamic changes between the groups when using dexmedetomidine and also with that of Kanazei et al. [29] who found comparable values of HR and MAP. They explained this by the use of low dose dexmedetomidine.

Vikas Dutta et al. who studied the effects of continuous paravertebral dexmedetomidine with ropivacaine on anesthetic drugs consumption, postoperative pain scores and postoperative analgesic requirements were in agreement with us in that they found a decrease in anesthetic drug consumption, better analgesia, and reduction of postoperative opioids consumption. However, they reported a significant decrease in HR and MAP in dexmedetomidine group. This can be explained by their use of a loading dose of dexmedetomidine in the form of 1 μ g/kg bolus dose [30].

Also in our current study, FEV1, FVC and PaO_2/FiO_2 ratio were significantly higher and $PaCO_2$ was significantly lower in G_{MD} and G_{PV} when compared with G_M indicating pulmonary function

improvement, better oxygenation, and ventilation when adding dexmedetomidine to morphine either IV or paravertebral.

Hidri Esme et al. who studied 45 patients for pain control after thoracotomy comparing intravenous analgesia versus intermittent paravertebral subpleural analgesia proved that intermittent paravertebral subpleural morphine is superior to intermittent paravertebral subpleural bupivacaine and intermittent systemic opioids as it provides better postoperative analgesia and surgical outcome. They also reported that FEV1 is significantly higher and rescue analgesia is significantly lower in paravertebral morphine group as compared with the systemic opioid group while no significant differences between the paravertebral bupivacaine group and systemic opioid group [31].

Mahmoud AAA, et al. who compared epidural analgesia against the continuous intravenous infusion of dexmedetomidine in patients with flail chest observed significantly higher PaO_2/FiO_2 ratio and significantly lower $PaCO_2$ in epidural group than continuous intravenous infusion group. Similarly, we observed that regional technique is superior to the intravenous one [32,33].

Conclusion

The addition of dexmedetomidine to morphine for TPVB and IV PCA provided better analgesia and improved spirometry in patients with MRF and also significantly decrease the total morphine consumption with less associated side effects. However, TPVB achieves more reduction in morphine consumption and better patient analgesia satisfaction than IV PCA.

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