e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2024; 16(2); 11-17

Original Research Article

Comparison of Continuous Intravenous Infusion of Tramadol and Intramuscular Diclofenac Sodium for Postoperative Analgesia

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Received: 03-11-2023 Revised: 11-12-2023 / Accepted: 20-01-2024
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Conflict of interest: Nil

Abstract

Background: This study was conducted to compare the efficacy of intramuscular diclofenac sodium with continuous intravenous infusions of tramadol for post-operative pain relief in patients undergoing major surgeries under regional anaesthesia. The side effects of the drugs are also compared.

Methods: This was a prospective randomized study conducted among 50 patients who underwent various gynecological, orthopedic, and general surgery at shree krishna hospital, karamsad from 2001 to 2003 (two years) after obtaining clearance from institutional ethical committee and written informed consent from study participants.

Results: Pre-operative values of mean pulse rates were comparable in the 2 groups, i.e. group A and group B. The difference in mean pulse rate between the two groups at 8 hours, 12 hours, 16 hours, 20 hours, and 24 hours was statistically significant. In changes in mean systolic BP at various time intervals, the difference in mean systolic blood pressure between the two groups at 15 minutes, 30 minutes, 4 hours, 6 hours, 12 hours, 20 hours, and 24 hours was statistically significant. In mean respiratory rate per minute at various time intervals, the difference in mean respiratory rates between the two groups at 15 minutes, 30 minutes, 4 hours, 6 hours, 12 hours, 20 hours, and 24 hours was statistically significant.

Conclusion: An intravenous bolus followed by an infusion of tramadol has no major advantage over intramuscular diclofenac sodium other than onset of action and ease of achieving the desired degree of analgesia.

Keywords: Intravenous Infusion, Tramadol, Intramuscular Diclofenac Sodium, Postoperative Analgesia

Introduction

Any method of postoperative analgesia must meet three basic criteria. It must be effective, safe and feasible. Recent advances in pharmacology have resulted in a number of new potent analgesics. Tramadol, a synthesised opioid of aminocyclohexanol group was developed by Grunethal in the 1960's and first introduced in Germany as a weak opioid with an atypical clinical profile. It is a pure agonist at mu, delta and kappa opioid receptors. The incidence of side effects from tramadol is dose-dependent and appears to be low compared to other opioids. Common side effects observed are dizziness, nausea, vomiting, and fatigue. If given LV too quickly, hot flushes and sweating may develop. Tramadol can be given orally, intramuscularly, intravenously, epidurally and intrathecally. The dose for adults should not exceed 600 mg/day. Diclofenac sodium was discovered by Ku et al. in 1975. Even in the present day, diclofenac sodium is a widely used analgesic for post-operative pain relief though an armament of analgesics is available. Non-steroidal anti-inflammatory drugs act mainly in the periphery to inhibit the initiation of pain signals whereas opioids act on specific opioid receptors in the central nervous system to attenuate the pain related signals. Diclofenac sodium is a highly potent member of the group of nonsteroidal anti-inflammatory drugs. Specific only to diclofenac sodium is the modulation of arachidonic acid release and uptake, which results in a dual inhibitory effect on both cyclooxygenase and lipoxygenase pathways, which

leads to a decrease in the synthesis of prostaglandin, prostacyclin and thromboxane which mediates postoperative pain and inflammation. The clinical study was undertaken to compare the efficacy and side effects of "intramuscular diclofenac sodium and continuous intravenous infusion of Tramadol for post-operative pain relief in adult patients undergoing major surgeries under regional anaesthesia.

Aims and Objectives

- To compare the efficacy of intramuscular Diclofenac sodium with continuous intravenous infusions of tramadol for post-operative pain relief in patients undergoing major surgeries under regional anaesthesia.
- The side effects of the drugs are also compared.

Materials & Methods

This was a prospective randomized study conducted among 50 patients who underwent various gynaecological, orthopaedic, and general surgery at Shree Krishna Hospital, Karamsad from 2001 to 2003 (two years) after obtaining clearance from institutional ethical committee and written informed consent from study participants.

Statistical Methods

Data was entered in MS Excel and analysed using SPSS software. Results were presented as tables.

Results

Table 1: Demographic Distribution

Age in Group	A	%	B	%
20-29	6	24	3	12
30-39	12	48	8	32
40-49	6	24	12	48
50-59	1	4	2	4
Age Distribution				
Sex	**A**	**%**	**B**	**%**
Male	10	40	12	48
Female	15	60	13	52
Total	25	100	25	100
Sex Distribution				

All the patients were in the age group ranging from 20 to 60 years. The majority of patients in group A were 30-39 years old (48%), while the majority of patients in group B were 40-49 years old (48%).
In group A, 40% were male patients and 60% were female patients. In group B, 48% were male patients and 52% were female patients.

Table 2

Time	Group	
	A	B
Pre-op	80.32	76.4
0 m	92.68	89.76
15 m	86.12	88.96
30 m	82.24	84.16
1 hr.	80	78.48
2 hr.	78.72	76.48
4 hr.	76.4	76.24
6 hr.	73.6	78.64
8 hr.	73.2	80.4
12 hr.	73.36	77.68
16 hr.	72.64	80.08
20 hr.	71.6	76.72
24 hr.	71.92	79.28

Changes in Cardiovascular Parameter (Mean Pulse Rate/Min at Various Time Interval)

Duration	Mean		SD		Z-Values	P-Values	Significance
	A	B	A	B			
Preoperative	80.32	76.4	10.04	6.58	1.538	0.124	NS
0 m	92.68	89.76	11.4	9.01	0.6821	0.7524	NS
15 m	86.12	88.96	11.24	9.22	-1.334	0.0911	NS
30 m	82.24	84.16	11.39	9.5	-0.875	0.1906	NS

1 hr.	80	78.48	11.78	8.15	0.3799	0.648	NS
2 hr.	78.72	76.48	9.642	6.96	0.9932	0.8397	NS
4 hr.	76.4	76.24	10.65	7.15	-0.4286	0.3341	NS
6 hr.	73.6	78.64	10.2	7.87	-2.1911	0.0142	NS
8 hr.	73.2	80.4	9.167	6.16	-3.0946	0.001	S
12 hr.	73.36	77.68	9.032	6.85	-2.1629	0.0153	S
16 hr.	72.64	80.08	8.22	6.79	-3.2497	0.0006	S
20 hr.	71.6	76.72	7.348	7.59	-2.2504	0.0122	S
24 hr.	71.92	79.28	7.713	6.11	-3.487	0.0002	S
Wilcoxon Rank-Sum Test Applied to Cardiovascular Parameter (Pulse Rate/Min)							
NS- Not Significant, S-Significant							

Pre-operative values of mean pulse rates were comparable in 2 groups (p>0.05) i.e., in group A it was 80.32/minute and in group B it was 76.4/minute. At 0 minutes, when patients complained of pain in group A, the mean pulse rate increased to 92.68/minute, in group B, it increased to 89.76/minute, which was clinically significant. Afterwards, a gradual fall in pulse rate was noticed in group A, at 4 hours it was 76.4/minute, at 16 hours it was 72.64/minute and at 24 hours it was 71.92/minute. These changes were clinically insignificant. In group B, at 15 minutes the pulse rate was 88.96/minute. This change was clinically significant and at 4 hours it was 76.24/minute. Afterwards, a rise was noticed, at 6 hours it was 78.64/minute, at 8 hours it was 80.4/minute, at 16 hours it was 80.08/minute and at 24 hours it was 79.28/minute. These changes were clinically insignificant. The difference in mean pulse rate between the two groups at 8 hours, 12 hours, 16 hours, 20 hours and 24 hours was statistically significant.

Table 3

Time	**Group**	
	A	**B**
Pre-op	120.72	118.48
0 m	132.72	131.12
15 m	124.24	129.84
30 m	117.84	124.88
1 hr.	117.2	120.64
2 hr.	116.48	119.28
4 hr.	113.52	118.96
6 hr.	110.9	120.72
8 hr.	109.28	123.2
12 hr.	108.8	1220.8
16 hr.	109.2	122.24
20 hr.	110	119.04
24 hr.	110.4	120.36

Changes in Mean Systolic BP at Various Time Interval							
Duration	**Mean**		**SD**		**Z-Values**	**P-Value**	**Significance**
	A	**B**	**A**	**B**			
Preoperative	120.72	118.48	9.2715	8.78	0.4213	0.6632	NS
0 m	132.72	131.12	7.6131	8.526	0.6167	0.7313	NS
15 m	124.24	129.84	11.363	8.184	-2.117	0.0171	S
30 m	117.84	124.88	12.395	8.546	-2.1976	0.014	S
1 hr.	117.2	120.64	13.589	7.952	-01.9747	0.1649	NS
2 hr.	116.48	119.28	12.142	7.786	-1.337	0.0906	NS
4 hr.	113.52	118.96	8.8182	8.126	-2.2748	0.0115	S
6 hr.	110.9	120.72	9.221	6.554	-3.6798	0.0001	S
8 hr.	109.28	123.2	8.8484	7.416	-4.6663	0	NS
12 hr.	108.8	122.08	9.6609	5.53	-3.8506	0.0001	S
16 hr.	109.2	122.24	9.2195	5.869	-4.8156	0	NS
20 hr.	110	119.04	8.641	8.126	-3.3569	0.0004	S
24 hr.	110.4	120.36	9.363	9.142	-3.3796	0.0004	S
Wilcoxon Rank-Sum Test Applied to Cardiovascular Parameter (Systolic BP)							
NS- Not Significant, S-Significant							

Pre-operative values of mean systolic blood pressure were comparable in 2 groups (p>0.05); in group A, it was 120.72 mmHg and in group B, it was 118 mmHg. At 0 minutes when patients complained of pain in group A, the mean systolic blood pressure increased to 132.72 mmHg and in group B, it increased to 131.12 mmHg. Afterwards, a gradual fall in systolic blood pressure was noticed in group A. At 4 hours it was 113.52 mmHg, at 16 hours it was 109.2 mmHg and at 24 hours it was 110.4 mmHg. These changes were clinically insignificant. In group B, a fall in systolic blood pressure was noticed at 4 hours, which was 118.96 mmHg. Afterwards a rise was noticed at 6 hours i.e. 120.72 mmHg, at 8 hours 123.2 mmHg, at 16 hours 122.24 mmHg and at 24 hours it was 120.36 mmHg. These changes were clinically insignificant. The difference in mean systolic blood pressure between the two groups at 15 minutes, 30 minutes, 4 hours, 6 hours, 12 hours, 20 hours, 24 hours was statistically significant.

Table 4

Time	Group	
	A	B
Pre-op	21.36	22.96
0 m	26.32	26.64
15 m	24	25.84
30 m	22.16	23.52
1 hr.	21.64	21.04
2 hr.	20.84	20.64
4 hr.	19.84	20.56
6 hr.	19.36	21.36
8 hr.	19.68	22.8
12 hr.	19.28	21.12
16 hr.	19.44	22.72
20 hr.	19.2	20.88
24 hr.	19.44	21.76

Mean Respiratory Rate (per minute) at Various Time Interval

Duration	Mean		SD		Z-Values	P-Value	Significance
	A	B	A	B			
Preoperative	21.36	22.96	2.361	1.65	0.6255	0.7342	NS
0 m	26.32	26.64	3.5	2.93	-0.8247	0.2048	NS
15 m	24	25.84	3.367	2.94	-2.0623	0.0196	S
30 m	22.16	23.52	2.824	2.26	-2.1424	0.0161	S
1 hr.	21.64	21.04	2.498	2.01	0.8418	0.8001	NS
2 hr.	20.84	20.64	2.192	1.6	0.3142	0.6233	NS
4 hr.	19.84	20.56	1.625	1.08	-1.9578	0.0251	S
6 hr.	19.36	21.36	1.977	1.98	-3.3052	0.0005	S
8 hr.	19.68	22.8	1.887	2.24	-4.2773	0	NS
12 hr.	19.28	21.12	1.514	2.01	-3.2427	0.0006	S
16 hr.	19.44	22.72	1.781	1.99	-4.7145	0	NS
20 hr.	19.2	20.88	1.528	1.74	-3.6716	0.0001	S
24 hr.	19.44	21.76	1.474	2.26	-3.5972	0.0002	S

Wilcoxon Rank-Sum Test Applied to Respiratory Rate

NS-Not Significant, S-Significant

Pre-operative values of mean respiratory rates were comparable in 2 groups (p>0.05), i.e., in group A it was 21.36/minute and in group B it was 22.96/minute. At 0 minutes when patients complained of pain in group A, the mean respiratory rate increased to 26.32/minute and it increased to 26.64 per minute in group B. Afterwards, a gradual fall in respiratory rate was noticed, at 4 hours it was 19.84/minute in group A and 20.56/minute in group B. Then there was no significant change in respiratory rate in group A. In group B, a rise was noticed at 6 hours which was 21.36/minute, at 8 hours it was 22.8/minute, at 16 hours it was 22.72/minute and at 24 hours it was 21.76/minute. These changes were clinically insignificant. The difference in mean respiratory rates between the two groups at 15 minutes, 30 minutes, 4 hours, 6 hours, 12 hours, 20 hours, and 24 hours was statistically significant.

Table 5: Pain Score in Post-Operative Period VAS Mean

Time	Group	
	A	B
0 m	3	2.8
15 m	1.64	2.68
30 m	0.6	1.92
1 hr.	0.36	0.08
2 hr.	0.28	0
4 hr.	0.16	0
6 hr.	0.12	0.52
8 hr.	0	1.36
12 hr.	0	0.2
16 hr.	0	0.84
20 hr.	0	0.04
24 hr.	0	0.68

Post-operatively at 0 minutes, i.e. the time at which patients complained of pain, the mean pain score (VAS) in group A was 3, and in group B it was 2.8. Tramadol or diclofenac sodium injections were injected at this point, depending on the group. In group A, tramadol infusion injection was adjusted according to the patient's response, and in group B, diclofenac sodium injection was given 6-8 hours a day to maintain pain-free conditions for the first 24 hours of the post-operative period (VAS < 3). In group A, after starting tramadol infusion injection, a gradual fall in mean pain score was noticed, at 4 hours it was 0.16, at 16 hours it was zero and at 24 hours it was zero. The total dose of tramadol was recorded in all patients. The mean bolus dose of injection tramadol in our study was 47.48 mg, and the mean infusion dose was 9.49 mg per hour. In group B, after giving diclofenac sodium injection, a gradual fall in the mean pain score was noticed, at 4 hours it was zero. Afterwards, a rise was noticed; at 6 hours it was 0.52, at 8 hours it was 1.36, at 16 hours it was 0.84 and at 24 hours it was 0.6. The total dose of diclofenac sodium was recorded in all the patients and the mean bolus dose of diclofenac sodium injection in our study was 51.2 mg. 8 hrly. The difference in mean pain scores between the two groups was statistically not significant (p-value = 0).

Discussion

A clinically significant rise in pulse rate in group B at 0 and 15 minutes was due to the slow onset of action of the intramuscular injection of diclofenac sodium. This observation was supported by a study conducted by Al-Waili NS (2001) [1] on post caesarian patients and by Swadia VN, Shah MB (1999).[2] The difference in mean pulse rate between the two groups at 8 hours, 12 hours, 16 hours, 20 hours, and 24 hours was statistically significant.

The rise in mean pulse rate in group B is due to the wearing off of the analgesic effect of intramuscular diclofenac sodium.

The preoperative values of mean systolic blood pressure in group A was 120.72 mmHg and in group B it was 118 mmHg. At 0 minutes, when patients complained of pain in group A, the mean systolic blood pressure increased to 132.72 mmHg and in group B, it increased to 131.12 mmHg. Afterwards, a gradual fall in systolic blood pressure was noticed in group A. At 4 hours it was 113.52 mmHg, at 16 hours it was 109.2 mmHg and at 24 hours it was 110.4 mmHg. These changes were clinically insignificant. This gradual fall in blood pressure was due to the alleviation of pain due to the continuous intravenous infusion of tramadol.

In group B, a fall in systolic blood pressure was noticed at 4 hours which was 118.96 mmHg. Afterwards, a rise was noticed, at 6 hours it was 120.72 mmHg, at 8 hours it was 123.2 mmHg, 16 hours it was 122.24 mmHg and at 24 hours it was 120.36 mmHg. These changes were clinically insignificant. [2]

The difference in mean systolic blood pressure between the two groups at 15 minutes, 30 minutes, 4 hours, 6 hours, 12 hours, and 24 hours was statistically significant. The rise in mean systolic BP in group B is due to the wearing off of the analgesic effect of intramuscular diclofenac sodium. Diclofenac sodium injection was repeated after 6 to 8 hours.

These observations in change in mean pulse rate and systolic blood pressure was supported by Pieri M., Meacci, Santini et al. (2002), [3] Scott LJ, Perry CM et al. (2000), [4] Zackova, Taddei et al. (2001) [5] proving that there is no clinically significant change in mean pulse rate and systolic blood pressure in the postoperative period with tramadol.

Preoperative values of the mean respiratory rate in group A was 21.36/minute and in group B it was 22.96/minute. At 0 minutes, when patients complained of pain in group A mean respiratory rate increased to 26.32/minute and in group B, it

increased to 26.64/ minute. Afterwards, a gradual fall in respiratory rate was noticed, at 4 hours it was 19.84/minute in group A and 20.56/minute in group B. Then there was no significant change in respiratory rate in group A. In group B, a rise was noticed at 6 hours which was 21.36/minute, at 8 hours it was 22.8/minute, at 16 hours it was 22.72/minute and 24 hours it was 21.76/minute. These changes were clinically insignificant. The difference in mean respiratory rate between the two groups at 15 minutes, 30 minutes, 4 hours, 6 hours, 12 hours, 20 hours, and 24 hours was statistically significant.

The gradual fall in mean respiratory rate was due to the relief of pain and continuous infusion of tramadol in group A. Even though a fall in respiratory rate was noticed with tramadol the respiratory rate remained within the normal limit. No patients showed any degree of respiratory depression. The rise in mean respiratory rate in group B is due to the wearing off of the analgesic effect of intramuscular diclofenac sodium.

These observations in the change in mean respiratory rate were similar to those of the study conducted by Bloch MB, Dyer RA et al. (2002); [6] Silvasti M, Tarkkila Petal (1999); [7] Zackova M, Taddie S, et al. (2001); Scott LJ, Perry CM, et al. (2000); Pieri M, Meacci L et al. (2002).

Postoperatively at 0 minutes, i.e., the time at which patients complained of pain, the mean pain score in group A was 3 and in group B it was 2.8, as patient was instructed to inform the doctors immediately with the onset of mild pain. In group A, after starting injections of tramadol, a fall in the mean pain score was noticed within 15 minutes. The rate of infusion was increased if the patient complained of pain. The total dose of tramadol was recorded in all patients. The mean bolus dose of injection tramadol in our study was 47.48 mg, and the mean infusion dose was 9.49 mg./hr.

The mean VAS in group A, which was 1.64 at 15 minutes, remained significantly low for 24 hours as per shown in table. The dose at which the patient showed adequate analgesia did not have a significant depressant effect on pulse rate, blood pressure or respiratory rate. This gradual decrease in mean VAS within 15 minutes of starting tramadol infusion shows that intravenous bolus followed by infusion are better than single bolus dose of tramadol. This observation was supported by Rud U., Fischer et al. (1994) [8] who observed that infusion of tramadol was better than bolus injection and that 76.6% of patients assessed pain relief as excellent or good.

In another study, Griesinger, Rosch W et al. (1997) [9] found that continuous infusion of tramadol is a simple and safe procedure following major urological surgeries in children.

Bloch MB, Dyer RA et al. in their study concluded that tramadol bolus followed by infusion are as effective as epidural morphine. Scott LJ, Perry CM (2000) observed in their study that parentral tramadol effectively relieved moderate to severe pain and could be used in patients in whom nonsteroidal anti-inflammatory drugs are not recommended.

In group B, after giving diclofenac, a fall in the mean pain score was noticed. At 15 minutes, a slight decrease in mean pain score was noticed; afterwards, mean pain score remained significantly low up to 6 hours (VAS-0.52). At 8 hours (VAS-1.36) with a no complaint of pain, the patient was given diclofenac sodium, and it was repeated at 16 hours (VAS-0.84) and 24 hours (VAS-0.68). The total dose of diclofenac sodium was recorded in all the patients and the mean bolus dose of injection diclofenace in our study was 51.2 mg/8 hourly.

The difference in mean VAS between groups A and B was not significant clinically or statistically. Where statistical analysis was done by two-sample Kolmogorov-Smirnov test. No patients needed rescue analgesia in group B.

In our study, the median time for the second dose of diclofenac sodium was 360-480 minutes, which is not comparable with the study conducted by Wilder-Smith CH, Hill L et al. (2003) who observed that the time to the second postoperative rudemand for diclofenac sodium was 35-270 minutes.

In our study, the mean pain score in first hour decreased from 2.8 to 0.08 in group B. A study conducted by Al-Waili N. S. (2001) saw a decrease in mean pain score in 1 hour from 7.09 to 0.8 after diclofenac sodium.

Swadia V. N., Sha MB (1999) in their study. came to the conclusion that there is an equivalent degree of pain relief and duration of analgesia if tramadol and diclofenac sodium are given through the same route. Carlborg L. and Lindoff C. (1987) [10] compared the duration of action of diclofenac with pethidine and found that diclofenac gave significantly longer pain relief than pethidine.

Buchanan J. M., Baldasera et al. (1990) [11] found that diclofenac was more effective than papaveretum in pain control, wound tenderness, awareness and mobilization.

Patients were observed for side effects of drugs, like nausea, vomiting, and epigastric pain. In group A, the incidence of nausea was 40%, vomiting was 36% and 24% did not show any side effects. The patients who had nausea or vomiting were treated with injection of ondansetrone, but sedation was

not seen in the dose at which tramadol was given in our study. In group B, 32% showed epigastric pain, which was treated with a ranitidine injection. In group B, 68% of patients had no side effects. Other studies done in the past have also shown a variable incidence of nausea and vomiting after tramadol when used as a postoperative analgesic, which are as follows. Pieri M., Meacci L et al. (2002) found nausea in 22.6% of patients and vomiting in 8.5% of patients. Silvasti M, Tarkkila (1999) found nausea in 44% of patients in the tramadol group.

Conclusion

The analgesic effects of both tramadol and diclofenac are comparable. An intravenous bolus followed by an infusion of tramadol has no major advantage over intramuscular diclofenac sodium other than onset of action and ease of achieving the desired degree of analgesia.

Authors Contribution

Dr. Mohamed Hussain Sait A. : Drafting the article, Final approval of the version to be published and correspondence during publishing. Dr Antony K.A. : Critical revision of the article and manuscript correction.

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