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Propacetamol and Morphine in Postoperative Pain Therapy after Renal Transplantation

Mohammad Reza Khajavi, Atabak Najafi, Mehdi PanahKhahi and Reza Shariat Moharari
Medical Sciences/University of Tehran, Sina Hospital, Tehran, Iran

Abstract: The purpose of this study was to assess the analgesic efficacy and complication of intravenous propacetamol, compared with morphine after renal transplantation. In this randomized double blind study, 30 end stage renal disease candidates for renal transplantation from live donors, were divided into two groups: the first group (15 patients) received 2 g of propacetamol (IV), while the other group received 5 mg of morphine (IV). The intensity of pain and the complications were evaluated for 24 h (each 6 h). The mean intensity of pain in the group who received morphine was slightly lower than propacetamol at recovery (10 min after extubation) and 24 h following the operation. However, propacetamol showed significantly less adverse events. The analgesic efficacy of Morphine in controlling post operative pain in time (0) and 24 h following the operation was significantly greater than propacetamol whilst the latter showed less adverse effects during the study period.

Key words: Propacetamol, morphine, kidney transplantation, pain score

INTRODUCTION

Controlling postoperative pain reduces anxiety, somatic and autonomic reflexes and on the other hand, improves the function of the organs (Kehlet *et al.*, 2003; Heid and Jage, 2002). Many patients suffer from mild to moderate pain after renal transplantation; however, usage of morphine and meperidine in these patients is limited due to renal impairment: clearance of active metabolite of morphine (M6G) is kidney-related and as a result, the accumulation of these metabolites is common in patients with renal failure (Stein *et al.*, 2000; Katzung *et al.*, 2005). Therefore, these patients usually receive a little analgesia in post operative periods.

Several drugs have been administered to control pain in these patients (Mycek, 2000; Miller, 2000; Lahtinen *et al.*, 2002; Power, 2005). Propacetamol is a water-soluble analgesic used IV in order to relieve mild to moderate pain; using recommended doses every 4-6 h, it has a similar pharmacokinetics as morphine (Dahl *et al.*, 2000). The purpose of this study was to gauge the analgesic efficacy of propacetamol against morphine in order to assess their analgesic profile and complications after single and repeated administration.

MATERIALS AND METHODS

This randomized, double blinded, single centered study was conducted at Sina hospital, in Iran between

May 2005 and April 2006. The study was performed in accordance with the ethical principles of Helsinki declaration, after being approved in the ethics committee of the hospital.

Thirty End Stage Renal Diseased (ESRD) candidates for renal transplantation from live donors were studied. The patients were given a written informed consent and a detailed definition of the procedures and the used pain scales, before being enrolled.

Patients with a recent history of liver dysfunction, respiratory and cardiac insufficiency and any condition affecting the metabolism of the medications in this study were excluded. Patients with a history of alcohol or drug abuse, with known hypersensitivity to morphine or propacetamol were also excluded. It should be noted that the drugs confounding the quantification of analgesia (sedative, anxiolytics, antihistamine) were withheld the night prior to the surgery.

During the operation, 0.04 mg kg⁻¹ midazolam and 2 µg kg⁻¹ fentanyl were used as pre medication; general anesthesia was induced with 3-4 mg kg⁻¹ thiopental. Muscular relaxation for intubation and during surgery was achieved by atracurium. Anesthesia was maintained by oxygen (50%), nitrous oxide (50%), Isoflurane and supplementary fentanyl.

The mean duration of surgery was 2.5-3 h. At the end of the surgery and before the performance of the skin sutures, 2 g propacetamol (Bristol- Myers Squibb-Egypt) was infused (in 10 min) to 15 patients while others received 5 mg morphine IV (Daroo Pakhsh-Iran). The

patients were evaluated for pain score, blood pressure, heart rate, SPO2 and lab tests including: BUN, Cr, Uric acid, ALT, AST, Alb, PT, PTT, Ca, P and blood sugar during the 24 h following the operation by an anesthesiologist blind to the type of the anesthetic drug administered.

The patients were interviewed by the observer to obtain a self-assessment of the intensity of their pain based on a four point Verbal Rating Scale (VRS), 0, 1, 1.5, 3, 4.5, 6, 12, 18 and 24 h following the operation.

- 0 = no pain
- 1 = slight pain
- 2 = moderate pain
- 3 = severe pain

The rate of pain relief was assessed via a five point VRS, 24 h after the operation.

- 0 = complete pain relief
- 1 = good pain relief
- 2 = satisfactory pain relief
- 3 = unsatisfactory pain relief
- 4 = no pain relief

Re-injection was performed every 6 h (2.5 mg morphine IV (4 doses) or 1 g propacetamol IV infused in 10 min (4 doses)) on those with no acceptable response to the previous dose. Any adverse effects or complications were recorded, in both groups.

The gathered data were entered in SPSS version 11.5 and analyzed using chi-square and student t-test.

RESULTS

Thirty patients were studied in 2 groups and demographic and selected background characteristics were matched. The patients' age ranged from 18-60 years with the mean age of 40.3±11.2 years. Table 1 presents the demographic information of the two groups.

According to the 4 point VRS, intensity of pain was less in the morphine group compared with the other group at recovery (10 min after extubation) and 24 h after surgery (p<0.05 and p<0.04, respectively) (Fig. 1). There was no significant statistical difference reported between the intensity of pain during the times 0 and 24, in the two groups.

Morphine showed better pain relief in 5 point VRS, 24 h following the operation (0.87±0.52 VS, 1.8±0.95, p = 0.002). In other words, 73.3% of the patients who received morphine had complete or good pain relief in 24 h while only 53.3% of patients in the propacetamol group stated a complete or good response (p = 0.25) (Table 2).

Adverse events were reported in 17 and 10 patients of morphine and propacetamol group, respectively. (p<0.05) The most frequently reported adverse events are

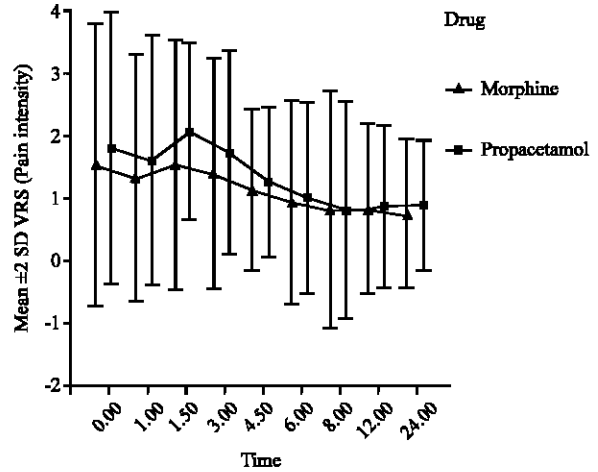


Fig. 1: Pain relief in each group according to the VRS system

Table 1: Demographic data and the intensity of pain at recovery of the enrolled patients in each group

Parameters	Morphine	Propacetamol	Total	
Age	40.2±11.6	40.47±11.2	40.33±11.2	
Gender	Male	9 (60)	8 (53.3)	
	Female	6 (40)	7 (46.7)	13 (43.3)
VRS	0	3 (20)	2 (13.3)	5 (16.7)
	1	5 (33.3)	4 (26.7)	9 (30)
	2	3 (20)	4 (26.7)	7 (23.3)
	3	4 (26.7)	5 (33.3)	9 (30)

Value in parenthesis show percentage

Table 2: The intensity of pain during the times 0 and 24 in each group

Time (h)	Morphine (n=15)		Propacetamol (n=15)		p-value
	Mean	Std. Deviation	Mean	Std. Deviation	
0	1.53	1.13	1.80	1.08	0.51
1	1.33	0.98	1.60	0.99	0.46
1.5	1.53	0.99	2.07	0.70	0.10
3	1.40	0.91	1.73	0.80	0.29
4.5	1.13	0.64	1.27	0.59	0.51
6	0.93	0.80	1.00	0.76	0.81
8	0.80	0.94	0.80	0.86	1.00
12	0.80	0.68	0.87	0.64	0.78
24	0.73	0.59	0.87	0.52	0.51

Table 3: Side effects in each group

Side effect	Morphine (%)	Propacetamol (%)	p-value
Nausea	6 (40)	3(20)	0.23
Vomiting	2 (13.3)	1 (6.7)	0.54
Constipation	6 (40)	1 (6.7)	0.03
Itching	2 (13.3)	1 (6.7)	0.54
Bradycardia	1 (6.7)	0	0.30
Pain in the injection site	0	4 (26.7)	0.032

Value without parenthesis show numbers

outlined in Table 3. Pain at the injection site was most common in the propacetamol group whilst nausea and constipation were frequently seen in those receiving morphine.

DISCUSSION

Acetaminophen is a central acting drug with analgesic effects, used to relieve mild to moderate pain such as headache (Varrassi *et al.*, 1999; Sinatra *et al.*, 2005). Propacetamol, a powder requiring reconstitution, is the intravenous form of acetaminophen. It is water-soluble, so it can be administered parenterally (2 g of propacetamol equivalent to 1 g of acetaminophen). Propacetamol is a rapid onset, so it can be used in order to reduce the intensity of pain during the first hours after operation (Beaussier *et al.*, 2005; Boccara *et al.*, 2005; Romsing *et al.*, 2002).

This study demonstrated no significant differences in the mean intensity of pain between the two groups in various intervals, while the mean intensity was reported to be lower in time zero (in recovery) and in 24 patients receiving IV morphine compared with the other group. These results correlate with those obtained in other studies comparing propacetamol and morphine. Vuilleumier *et al.* (1998) stated higher pain score in patients receiving 0.2 mg kg⁻¹ morphine compared with 30 mg kg⁻¹ propacetamol, following a general anesthesia. They concluded propacetamol to be a good substitute for morphine in preventing mild to moderate post-operation pain (Vuilleumier *et al.*, 1998). In another study, a decreased need to morphine and also a lower intensity of pain was showed in patients receiving propacetamol after spinal surgery (Hernandez-Palazon *et al.*, 2001).

On the contrary, some studies did not support these results. It has been shown that a significant pain relief was observed in patients receiving morphine or propacetamol compared with placebo; however, the study did not reveal a significant difference between morphine and propacetamol (Aken *et al.*, 2004). Some studies has also demonstrated that combine of NSAID and paracetamol has superior analgesia and pain relief compared with single drugs (Romundstad *et al.*, 2006).

Fewer adverse events were reported in the propacetamol group. The most common problem in patients receiving propacetamol was pain or local reaction in the administration site (26.7%), while as for the morphine group, nausea and constipation were more common (40%). Vomiting, pruritus and bradycardia were also more frequent in this group. Other adverse events of propacetamol as reported in other studies are: nausea and vomiting in 8.8-62%, injection site pain in 28-38% and injection site complications in 52% of the cases (Varrassi *et al.*, 1999; Boccara *et al.*, 2005; Aken *et al.*,

2004; Moller *et al.*, 2005). Gastrointestinal, cardiac and dermatic complications were reported less in our study compared with other studies, despite the fact that injection site pain was reported as like others (Aken *et al.*, 2004; Bannwarth *et al.*, 1992). Injection site pain after propacetamol infusion is thought to be due to low pH and high osmolarity of the solution (pH: 3.5, osmolarity: 410 mOsmol L⁻¹) which is different from the plasma (Miller, 2000; Lahtinen *et al.*, 2002).

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REFERENCES

- Aken, H.V., L. Thys, L. Veekman and H. Buerkle, 2004. Assessing Analgesia in single and repeated administrations of propacetamol for postoperative analgesia: Comparison with morphine after dental surgery. *Anesth. Analg.*, 98: 159-165.
- Bannwarth, B., P. Netter and F. Lopicque, 1992. Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol. *Br. J. Clin. Pharmacol.*, 34: 79-81.
- Beaussier, M., Weickmans, C. Paugam, S. Lavazais and J.P. Baechle *et al.*, 2005. A randomized, double blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. *Anesth. Analg.*, 100: 1309-1315.
- Boccara, G., A. Chaumeron, Y. Pouzeratte and C. Mann, 2005. The preoperative administration of ketoprofen improves analgesia after laparoscopic cholecystectomy in comparison with propacetamol or postoperative ketoprofen. *BJA.*, 94: 347-351.
- Dahl, V. and J.C. Reder, 2000. Non opioid postoperative analgesia. *Acta Anesth. Scand.*, 44: 1191-1203.
- Heid, F. and J. Jage, 2002. The treatment of pain in urology. *BJU Int.*, 90: 481-488.
- Hernandez-Palazon, J., J.A. Tortosa, J.F. Martinez-Lage and Perez-Florez, 2001. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. *Anesth. Analg.*, 92: 1473-1476.
- Katzung, B.G., 2005. *Pharmacology: Examination and Board Review*. 7th Edn., USA., Mc Graw Hill.

- Kehlet, H. and B.D. Jorgan, 2003. Anesthesia, surgery and challenges in postoperative recovery. *Lancet*, 362: 1921-128.
- Lahtinen, P., H. Kokki, H. Hendolin, T. Hakala and M. Hynynen, 2002. Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. *Anesth. Analg.*, 95: 813-819.
- Miller, R.D., 2000. *Anesthesia*. 5th Edn., Churchill Livingstone, pp: 273-373.
- Moller, P.L., S. Sindet-Pedersen, C.T. Petersen, G.I. Juhl, A. Dillenschneider and L.A. Skoglund, 2005. Onset of acetaminophen analgesia: Comparison of oral and intravenous routes after third molar surgery. *BJA.*, 94: 642-648.
- Mycek, M.J., 2000. *Lippincott's illustrated reviews pharmacology*. 2nd Edn., USA., LW & W.
- Power, I., 2005. Recent advances in postoperative pain therapy. *BJA.*, 95: 43-51.
- Romsing, J., 2002. Rectal and parenteral paracetamol and paracetamol in combination with NSAIDs, for postoperative analgesia. *BJA.*, 88: 215-226.
- Romundstad, L., A. Stubhaug, G. Niemi, L.A. Rosseland and H. Breivik, 2006. Adding propacetamol to ketorolac increases the tolerance to painful pressure. *Eur. J. Pain*, 10: 177-183.
- Sinatra, R.S., J.S. Jahr, L.W. Reynolds, E.R. Viscusi, S.B. Groundine and C. Payen-Champenois, 2005. Efficacy and safety of single and repeated administration of 1 g intravenous Acetaminophen injection (Paracetamol) for pain management after major orthopedic surgery. *Anesthesiology*, 102: 822-831.
- Stein, C., M. Schafer and H. Machelska, 2000. Why is morphine not the ultimate analgesic and what can be done to improve it? *J. Pain*, 1: 51-56.
- Varrassi, G., F. Marinangeli, F. Agro, L. Aloe, P. De Cillis and A. De Nicola *et al.*, 1999. A double blinded evaluation of propacetamol versus ketorolac in combination with patient controlled analgesia morphine: Analgesic Efficacy and Tolerability after Gynecologic Surgery. *Anesth Analg.*, 88: 611-616.
- Vuilleumier, P.A., T. Buclin and J. Biollaz, 1998. Comparison of propacetamol and morphine in postoperative analgesia. *Schweiz Med. Wochenscher*, 128: 259-263.