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The Addition of Metamizole to Morphine and Paracetamol Improves Early Postoperative Analgesia and Patient Satisfaction after Lumbar Disc Surgery

Parasetamol ve Morfine Metamizol Eklenmesi, Lumbar Disk Cerrahisi Sonrası Erken Postoperatif Analjezi ve Hasta Memnuniyetini Artırır

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ABSTRACT

AIM: Combined analgesic regimens produce sufficient analgesia by additive or synergistic effects, and reduce the total dose of analgesics and minimise adverse effects. We investigated the metamizole, paracetamol and morphine combination with respect to postoperative pain treatment in lumbar disc surgery.

MATERIAL and METHODS: After Ethics Committee approval and informed consent, 63 patients were allocated to three treatment groups; as Group paracetamol: paracetamol (1 g), Group paracetamol-metamizole: paracetamol (1 g) and metamizole (1 g), and Group placebo: no analgesic. All the patients received intravenous (i.v.) morphine with a patient-controlled analgesia device (PCA) as the rescue analgesic. Pain was assessed by the numerical pain rating scale (NRS, 0-3). Total morphine consumption at 24 hours, patient satisfaction and side effects were investigated.

RESULTS: NRS of Group paracetamol-metamizole was low at 15th min, 30th min and 1st hour, and the difference reached statistical significance at 30th min (p=0.033). Patient satisfaction at the same measurement times was high in this group. Total morphine consumption and side effects were not statistically different between the three groups.

CONCLUSION: Addition of metamizole to paracetamol along with iv morphine PCA offers an advantage over single iv morphine PCA and paracetamol, with respect to early postoperative pain treatment and patient satisfaction.

KEYWORDS: Non-narcotic analgesics, Paracetamol, Metamizole, Morphine, Lumbar disk surgery, Analgesics, non-narcotic

ÖZ

AMAÇ: Analjezik kombinasyonları, aditiv ve sinerjistik etkiler ile yeterli analjezi sağlarlar, ve total analjezik dozu ve yan etkilerde azalma olur. Biz çalışmamızda, metamizol, parasetamol ve morfin kombinasyonunun lumbar disk cerrahisi sonrası postoperatif ağrıya etkilerini araştırdık.

YÖNTEM ve GEREÇ: Etik komite izni ve aydınlatılmış onam formu alındıktan sonra, 63 hasta üç tedavi grubuna ayrıldı; Grup parasetamol: parasetamol (1 g), Grup parasetamol-metamizol: parasetamol (1 g), metamizol (1 g) ve Grup plasebo: hiçbir analjezik verilmedi. Bütün hastalara, ihtiyaç durumunda almak üzere, intravenöz morfin hasta kontrollü analjezi cihazı (HKA) bağlandı. Ağrı değerlendirmesi nümerik ağrı derecelendirme skalası (NRS, 0-3) ile yapıldı. 24 saatlik total morfin kullanımı, hasta memnuniyeti ve yan etkiler araştırıldı.

BULGULAR: Parasetamol-metamizol grubunun NRS değeri 15. Dak, 30. Dak ve 1. Saatte düşüktü, ancak 30. dak değeri istatistiksel olarak anlamlı farklıydı (p=0.033). Aynı ölçüm zamanlarına, hasta memnuniyeti bu grupta yüksek bulundu. Total morfin dozu ve yan etkiler açısından gruplar arası istatistiksel anlamlı fark yoktu.

SONUÇ: Parasetamol ve morfine, metamizol eklenmesi, tek morfin veya parasetamolden, erken postoperatif ağrı tedavisi ve hasta memnuniyeti açısından daha yararlıdır.

ANAHTAR SÖZCÜKLER: Narkotik olmayan analjezikler, Parasetamol, Metamizol, Morfin, Lumbar disk cerrahisi, Analjeziler:narkotik olmayan

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INTRADUCTION

Systemic administrations of analgesics is the most widely used method to reduce postoperative pain after lumbar disc surgery. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) play an important role in reducing postoperative pain (8). A combination of analgesics produces additive or synergistic effects and provides sufficient analgesia. Combined regimens can reduce the total dose of analgesics and minimize the adverse effects (4). The combination of opioid, NSAIDs and paracetamol reduces the postoperative opioid requirement and decreases the incidence of opioid-induced side effects (6). The paracetamol and NSAIDs combination is widely used clinically, but what this combination offers is still a matter of debate (19).

There are studies reporting that the addition of metamizole to morphine would potentiate morphine's antinociceptive effects (2, 9, 14). However, the combination of metamizole (NSAID), paracetamol and morphine has not been evaluated previously with respect to postoperative pain control after lumbar disc surgery.

Previous studies have investigated a combination of paracetamol with intravenous (i.v.) morphine patient-controlled analgesia (PCA). There are conflicting results about this combination with respect to its opioid-sparing effect (4, 11, 18).

The aim of this study was to investigate the effects of addition of i.v. metamizole to i.v. paracetamol along with i.v. morphine PCA in respect to total morphine consumption, pain alleviation and patient satisfaction after lumbar disc surgery.

MATERIAL and METHODS

After obtaining Ethics Committee approval and informed consent, 63 patients ASA I-II (American Society of Anesthesiologists), scheduled for single-level, unilateral lumbar disc surgery were informed about the use of the PCA device and the numeric pain rating scale (NRS). Patients with impairment in liver function, renal dysfunction, hypersensitivity or contraindication to the study drugs, or history of lumbar disc re-operations and the patients who would be operated on by residents were excluded. Only the operations of the senior experienced surgeons were included in the study.

Each patient was monitored in the operating room, to include electrocardiogram, noninvasive blood pressure measurements, and pulse oximeter use. Patients received a standard anesthetic regime. They were premedicated with 5 mg diazepam orally, half an hour before the anesthesia induction. Anesthesia was induced with propofol 2.5 $mg.kg^{-1}$, fentanyl 1 $\mu g.kg^{-1}$ and vecuronium 0.1 $mg.kg^{-1}$ i.v. and maintained with 2% sevoflurane in 50% N_2O/O_2. No fentanyl was administered in the last 30 minutes (min) of the surgery. At the end of the surgery, ondansetron 4 mg was administered to minimize postoperative nausea and vomiting. Neostigmine 0.05 $mg.kg^{-1}$ and atropine 0.01 $mg.kg^{-1}$ were administered for reversal of neuromuscular blockade.

Patients were randomized to one of three treatment groups in a double-blind manner using a computerized allocation schedule and unlabeled syringes. After randomization, an anesthetist not involved in the patients care or data collection, prepared the unlabeled syringes and gave them to the anesthetist dealing with the patient care. In Group paracetamol-metamizole (Group PM), 1 g paracetamol (Perfalgan, 10 $mg.ml^{-1}$) was infused by a perfusor set to deliver 400 $ml.hour^{-1}$ over 15 min to enable double blindness at the end of the operation and i.v. 1 g metamizole (Adepiron, 500 $mg.ml^{-1}$) was injected during the skin closure. In Group paracetamol (Group P), paracetamol 1g was infused in the same manner as in the previous group and 2 ml 0.9% NaCl i.v. was injected instead of metamizole. In Group placebo (Group C) no drug was administered. All the patients received morphine PCA as the rescue analgesic; loading dose 1 mg, bolus dose 1 mg, lock-out interval 10 min, 4 hour (h) limit 20 mg, no background infusion. The device was connected immediately to all groups upon arrival at the postanesthesia care unit. The time elapsed from the end of surgery to the beginning of PCA was approximately 10-15 min.

A blinded observer recorded pain, cumulative morphine consumption, adverse effects (nausea, vomiting, shivering, urinary retention) and patient satisfaction at postoperative 15 and 30 min, 1 h, 2 h, 6 h and 24 h.

Pain was evaluated by NRS as: 0: no pain, 1: mild pain, 2: moderate pain, and 3: severe pain.

Patient satisfaction with postoperative pain management was assessed by a 4-point rating scale as: 0: poor, 1: moderate, 2: good, and 3: excellent.

STATISTICAL ANALYSIS

The SPSS 15.0 for Windows statistical package (SPSS Inc., Chicago, IL, USA) was used for all analyses. Patient characteristics, duration of the procedure, pain scores, postoperative morphine consumption, and morphine requests were analyzed using analysis of variance, Kruskal-Wallis test and X^2-test, where appropriate. Normal distribution of numerical data was assessed using the Shapiro-Wilk test. Significance was determined at the $p<0.05$ level. The Bonferroni approach was used for multiple comparisons. Results are given as medians (range) for non-parametric data and as mean ± standard deviation (SD) for continuous data. The number of patients (approximately 20 patients per group) was assumed to detect (with 80% power and 5% type-1 error level) a 1-point difference in NRS scores (mean NRS score of 2 and assuming an SD of 1 in all groups) between the groups.

RESULTS

In total, the results of 63 patients were analyzed and no patient was excluded. Twenty patients were enrolled in Group C, 20 in Group P and 23 in Group PM. Patient characteristics, duration of surgery and anesthesia, and total intraoperative fentanyl use were similar among the groups (Table I).

We observed differences among the groups, with respect to NRS scores at 15 min, 30 min and 1 h, but the difference reached statistical significance only in the PM group at 30 min (Kruskal-Wallis test, p=0.033 with post hoc Mann-Whitney U tests having p values of 0.018 and 0.038 for comparisons versus Groups C and P, respectively, Figure 1). The scores were similar at observations beyond 1 h, i.e. at 2 h, 6 h and 24 h (Table II). Median NRS scores at 2 h were 1 (0-3) in all groups indicating mild pain.

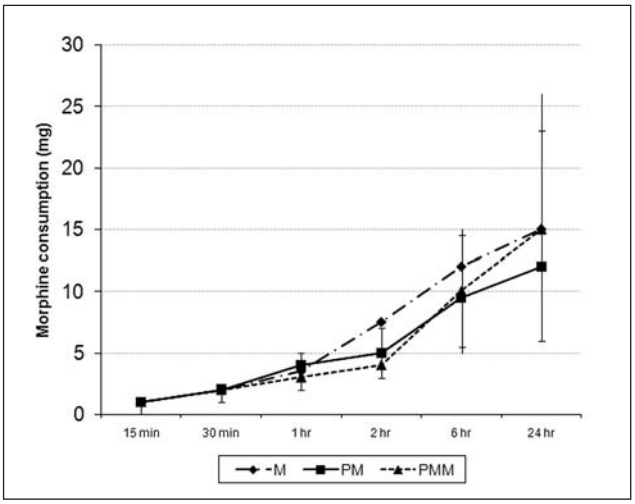

Figure 1: *Morphine consumption (mg) at 15 min, 30 min, 1 h, 2 h, 6 h and 24 h hour of the groups. Results are expressed as mean ± SD.*

In Group PM, cumulative morphine use in two patients at 6 h was 36 mg and 23 mg, causing an increase in 24 h morphine consumption (Figure 2). Total morphine use at 24 h was 23.6±19.3 mg, 15.6±11.7 mg and 18±12.8 mg in Groups C, P and PM respectively (not significant, Figure 1)

Patient satisfaction scores were significantly higher at 15 min, 30 min, 1 h and 2 h (Kruskal-Wallis test, p=0.005, 0.002, 0.003 and 0.042, respectively) in Group PM when compared with Groups P (Mann-Whitney U test, p=0.003, 0.001, 0.003 and 0.021, respectively) and C (Mann-Whitney U test, p=0.009, 0.009, 0.004 and 0.042, respectively) (Table III). Median patient satisfaction scores at 30th min were

Table I: Patients Characteristics and Duration of Surgery and Anesthesia and Total Peroperative Fentanyl Dose.

	Placebo Group	Paracetamol Group	Paracetamol-Metamizole Group	P
Age (yr)	46.8±12.7	48.8±9.6	48.7±10.5	NS
Weight (kg)	77.2±18.1	76.4±14.5	77.1±14.2	NS
Gender (M/F)	12/8	7/13	10/13	NS
Duration of surgery (min)	132.5±38	131.3±39.1	129.1±41.7	NS
Duration of anesthesia (min)	142.5±29	140±32.3	143±27.3	NS
Total peroperative fentanyl use (μg)	91±32.6	77±15.6	84±20	NS

Results were given as mean ±SD or numbers of patients. ***NS:*** *non significant,* ***P****>0.05*

Table II: Pain Assessment at 15 min, 30 min, 1 h, 2 h, 6 h and 24 h hour by Numerical Rating Scale (NRS, 0: no pain, 1: light pain, 2: moderate pain, 3: severe pain)

Numerical Rating Scale (NRS)	Placebo Group	Paracetamol Group	Paracetamol-Metamizole Group
NRS 15th min	2±0.5	2±0.5	2±0
NRS 30th min	2±0.5	2±1	1±1*
NRS 1st hour	2±0	2±0	1±1
NRS 2nd hour	1±0	1±0	1±0
NRS 6th hour	1±1	1±0.5	1±0
NRS 24th hour	1±0	1±0	0±0

*Results were given as median values±SD (*p=0.033, Paracetamol-Metamizole versus placebo and paracetamol groups)*

Table III: Patient Satisfaction Scores at 15 th, 30 th Minutes, 1st, 2nd, 6th and 24 th Hours.

Patient Satisfaction (PS)	Placebo Group	Paracetamol Group	Paracetamol-Metamizole Group
PS 15th min	1±1	1±1	2±0*
PS 30th min	1.5±1	1±0	2±1*
PS 1st h	2±1	2±0	3±0*
PS 2nd h	2±0.5	2±0.5	3±0*
PS 6th h	3±1	2.5±0.5	3±0
PS 24th h	3±0	3±0	3±0

*Results were expressed as median±SD (*p=0.005, 0.002, 0.003, 0.042 at 15 min, 30 min, 1 h and 2 h, respectively, Paracetamol-metamizole versus placebo and paracetamol groups).*

1.5 (0-3), 1 (0-3), 2 (1-3) in Groups C, P, PM respectively and increased to 3 at 24 h in all groups.

Morphine demand in Group C was higher than in the other groups at all evaluation times with no statistical significance (Figure 2). In Group C, one patient's morphine demand was 941 and two patients' demand was 398, causing an extreme increase in the total number of demands.

There were no statistically significant differences in the incidence of nausea, vomiting, shivering, or urinary retention between the groups (Table IV).

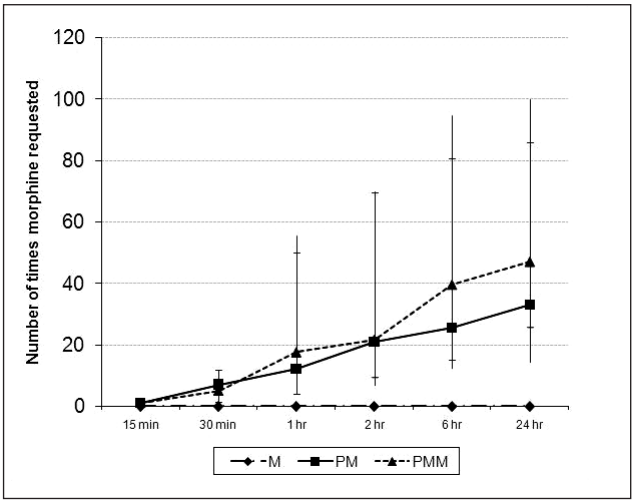

Figure 2: *Morphine request (number) at 15 min, 30 min, 1 h, 2 h, 6 h and 24 h of the groups. Results are expressed as mean ± SD.*

DISCUSSION

This study showed that pain control was similar with the combination of iv paracetamol and i.v. morphine PCA compared to i.v. morphine PCA alone, but addition of metamizole provided better the early pain scores in the first postoperative two hours and increased patient satisfaction. In the early postoperative period, combination of metamizole and paracetamol with morphine PCA provided better pain control and better patient satisfaction.

NSAIDs and paracetamol have been widely used for multimodal analgesia in the postoperative period (4, 19). NSAIDs show their effects by inhibiting peripheral cyclooxygenase (COX). The COX enzyme has COX-1 and COX-2 subtypes. NSAIDs reduce

Table IV: The Frequency of the Side Effects.

	Placebo Group	Paracetamol Group	Paracetamol-Metamizole Group	P
Nausea	3 (15%)	5 (25%)	3 (13%)	NS
Vomiting	3 (15%)	2 (10%)	2 (8.7%)	NS
Shivering	0 (0%)	1 (5%)	1 (4.3%)	NS
Urinary retention	0 (0%)	1 (5%)	2 (8.7%)	NS

Results were given as number of patients (%). NS: non significant P>0.05

prostaglandin synthesis in peripheral tissues by inhibition of the COX enzyme in the arachidonic acid metabolism (8, 19). Metamizole is a non-selective COX-2 inhibitor with good tolerability. COX-2 inhibitors are thought to have a lower risk/benefit ratio than traditional NSAIDs (8). In recent studies, COX-3 has been described as a variant of COX-1, which has a role in the paracetamol mechanism (20, 23). The combination of paracetamol with diclofenac, ketoprofen, ketorolac, suprofen and tenoxicam provided more effective analgesia than paracetamol alone (7, 12, 15).

Paracetamol is a relatively safe nonopioid analgesic despite hepatic cell injury following high-dose administration (22). Paracetamol interacts with the serotonergic system and is a centrally acting inhibitor of COX. It may be used alone or in combined analgesic regimens for the treatment of mild and moderate postoperative pain (4, 11). Oral, rectal and in i.v. forms of paracetamol have been available. In this study, the combination of paracetamol with metamizole and morphine PCA was investigated. Single-dose metamizole at the end of the operation along with paracetamol and morphine PCA provided better pain control. Repeated doses of metamizole would possibly provide prolonged pain control.

Metamizole is a pyrazoline-derived non-opiate analgesic drug with antipyretic and spasmolytic features. It is a widely used injectable nonopioid analgesic for postoperative pain therapy in several European countries with a low incidence of adverse reactions, but a risk of agranulocytosis. The incidence of this side effect is a matter of debate (5) and may be dependent on genetic factors, and the real incidence of agranuloscytosis due to metamizole is not known (8). Metamizole is not approved for pain therapy in the United States and Scandinavian countries. Agranulocytosis was not observed in our study group or during daily routine practice. It is widely used in our hospital with no known agranulocytosis effect. Metamizole has limited contraindications that are mostly related to the gastro-intestinal tract as common to all NSAIDs (2,12). Metamizole's analgesic effect starts almost immediately after its i.v. administration and reaches its peak in 20 to 45 minutes. Methyl-amino-antipyrine and aminoantipyrine are its active metabolites. The half-life of methyl-amino-antipyrines is about 2.7 hours. Postoperative analgesia for two hours was improved with metamizole in our study, and this two-hour period is consistent with its half-life.

The effect of i.v. paracetamol on postoperative analgesia is a questionable. Sinatra et al. (21) found that visual analogue scale (VAS) score and morphine consumption were decreased, while side effects were not changed in the postoperative 24 hours following 1 g i.v. paracetamol and 2 g i.v. proparacetamol in patients undergoing major orthopedic surgery. Hernandez-Palazon et al.(10) gave 2 g proparacetamol per 6 hours for 3 days following spinal fusion surgery, and found that morphine consumption and pain score were significantly decreased. Many studies have found that addition of paracetamol to morphine did not decrease the pain score or morphine consumption (4, 8, 18). The effect of non-opioid analgesics is dependent on the type of surgery performed. After retinal surgery, the analgesic potency of paracetamol is comparable to that of metamizole (13), whereas after lumbar microdiscectomy, the analgesic potency of paracetamol was inferior to metamizole (8). In contrast with the mentioned study, we added metamizole to paracetamol and found a more pronounced pain relief after lumbar discectomy. We found no difference between placebo and paracetamol groups in respect to postoperative pain

treatment. This result was similar to that of Grungmann et al (8). It was expected that total morphine consumption would be lowest in Group PM as NRS of scores of pain were better in the early postoperative period. Although not significant, Group PM's morphine use was higher than expected. This is because two patients in Group PM used 36 mg and 23 mg morphine at 6 h (cumulative dose) hour causing an increase in total 24 h morphine use.

The PCA device lock-out period was 10 min and a 4 h limit was set to 20 mg (1 h morphine limit 5 mg and 24 h limit 120 mg). No patient in the study used 120 mg morphine in the 24 h period in any group. The maximum doses used in 24 h were 55 mg in Group C (one patient), 44 mg in Group P (one patient) and 42 mg in Group PM (one patient).

Hernandez- Delgadillo et al (9) found that single and repeated doses of metamizole increased the duration of the antinociceptive effects of morphine and potentiated its effects. The mechanisms of the acute antinociceptive synergistic effects of metamizole and morphine are not known. Peripheral activation of the arginine-nitric oxide-cyclic guanosine monophosphate pathway may play a role in the antinociceptive synergistic effects of morphine and metamizole (1). In our study, metamizole was administered once at the end of the operation. Although total morphine consumption in 24 hours was the same in all groups, early pain control was better in the PM group, and this may be due in part to the synergistic effect of metamizole and morphine. Further studies should be conducted to investigate the 24 h morphine use if metamizole is given in repeated doses to patients undergoing lumbar disc surgery. According to Montané's (17) review article on postoperative pain therapy after traumatic orthopedic surgery (TOS), evidence regarding pain therapy after TOS was insufficient to identify the best method. It was mentioned that single-dose regimens of drugs were mostly studied, as in our study. This was the usual practice in our hospital, while prolonged postoperative pain therapy was usually under the purview of the neurosurgical department. Thus, the results of the study might be more easily applicable to routine clinical practice. The safety, route of administration, and length of action of the drug should be taken into consideration for the best treatment option.

The addition of paracetamol to morphine was previously shown to have no beneficial effect in decreasing morphine consumption, and this was also supported by our results (4, 8, 18). Additionally, this study showed that addition of metamizole at the end of the surgery to the combination of paracetamol-i.v. morphine PCA was useful in reducing pain scores in the early postoperative period while increasing patient satisfaction.

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