Renal function after laparoscopic cholecystectomy and analgesia with tramadol and dipyrone or ketorolac

Tiago Pechutti Medeiros¹, Pedro Thadeu Galvão Vianna², Leopoldo Muniz da Silva³, Lidia Raquel de Carvalho⁴, Gilberto Elias Wady⁵, Leandro Gobbo Braz², Yara Marcondes Machado Castiglia²*

¹Graduate Program in Anesthesiology, Botucatu Medical School, UNESP-Universidade Estadual Paulista, Botucatu, Brazil
²Department of Anesthesiology, Botucatu Medical School, UNESP-Universidade Estadual Paulista, Botucatu, Brazil;
³Corresponding Author: varac@fmb.unesp.br
⁴São Luiz Hospital, São Paulo, Brazil
⁵Department of Biostatics, Institute of Biosciences, UNESP-Universidade Estadual Paulista, Botucatu, Brazil

Received 4 September 2013; revised 12 October 2013; accepted 28 October 2013

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ABSTRACT

Background: Laparoscopic cholecystectomy (LC) reduces surgical trauma and hospital stay, but requires effective and safe postoperative analgesia. This prospective and double-blind study investigated the effects of analgesia with tramadol combined with either dipyrone or ketorolac on the postoperative renal function of patients submitted to LC. Methods: Pre- and post-operatively (PO), estimated glomerular filtration rates (GFR), obtained by two formulas dependent on blood Cr and one on blood cystatin C values, and tubular enzymuria—alkaline phosphatase (AP), γ-glutamiltransferase (γ-GT)—were determined in well hydrated patients who underwent LC and analgesia with tramadol combined with either dipyrone (Dipyrone, n = 63) or ketorolac (Ketorolac, n = 63). Upon discharge from the post-anesthetic care unit (PACU), pain (through Verbal Numerical Scale—VNS) and need for rescue analgesia with morphine were evaluated. Results: There was hemodilution PO, which made GFR profile analysis more difficult—those dependent on Cr increased and statistically correlated, but those dependent on cystatin C did not change. There was a significant PO increase in AP in the Dipyrone and Ketorolac groups, and in the product of the both enzymes in the Ketorolac group. Upon PACU discharge, the Dipyrone group showed significantly higher VNS scores than the Ketorolac group. All patients received morphine PO, and the total dose needed for pain control differed between groups, but without statistical significance. Conclusions: The association of tramadol with dipyrone or ketorolac in well hydrated patients submitted to LC had similar analgesic effectiveness in the PACU. Postoperatively, the effect on GFR may have been masked by hemodilution, and enzymuria was discreetly enhanced when ketorolac was used.

Keywords: Kidney Function Tests; Pneumoperitoneum; Biological Markers; Cystatin C; Ketorolac; Analgesia

1. INTRODUCTION

Renal venous pressure, hydrostatic pressure and glomerular filtration rate (GFR) are adversely affected by pneumoperitoneum. However, expansion of the extracellular volume can be beneficial to renal function [1-3]. Pain after laparoscopic surgery is multifactorial and may be quite intense. Current pain management relies on a number of strategies, including the concomitant use of opioids and anti-inflammatory drugs [4]. Remifentanil, a synthetic opioid used in anesthesia, has a predictable duration of action (elimination half-life of 8 - 20 minutes) because it is metabolized via plasma esterases [5]. While reducing opioid-induced adverse ef-
fects, remifentanil does not provide residual analgesia at the immediate postoperative period. Tramadal is a centrally acting analgesic that consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms: (+)-tramadol and the metabolite (+)-0-desmethyl-tramadol are agonists of μ opioid receptor. (+)-tramadol inhibits serotonin re-uptake, and (−)-tramadol inhibits norepinephrine re-uptake, increasing the inhibitory effects on pain transmission in the spinal cord [6]. It is excreted via the kidney (over 30%), and in bolus doses and various injections it does not affect renal blood flow in normal rats [7]. Tramadol and non-steroidal anti-inflammatory drugs (NSAID) have often been combined for the clinical treatment of post-operative pain. However, the stimulation of opioid receptors may increase pain sensitivity immediately after opioid administration (opioid-induced hyperalgesia). Therefore, investigating the effects of combining opioids with non-opioid analgesics, including NSAIDs, would be of especial interest for anesthesia researchers [8].

NSAIDs block the enzyme cyclooxygenase (COX) and, in consequence, the synthesis of renal vasodilator prostaglandins (PG) [9], which help maintain renal blood flow and GFR, modulating the vasoconstrictor effects of angiotensine II or norepinephrine [10]. However, in rats anesthetized with sodium pentobarbital, the NSAID ketoprofen, administered early after hypotension due to hemorrhage, caused fewer changes in renal function and histology than the barbiturate [11].

Serum cystatin C level, an early marker of mild GFR deterioration [12], is a useful endogenous alternative to estimate GFR. However, in a study including 8058 individuals aged 25 - 75 years, besides not being superior to creatinine in measuring GFR, serum cystation C seemed to be influenced by factors other than kidney function alone [13]. To measure the integrity of tubular cells, assessing urinary concentrations of renal enzymes is a sensitive non-invasive method. These renal enzymes are located on specific sites of the kidney: γ-glutamyltransferase (γ-GT) is mainly found in the tubules near the loop of Henle, while alkaline phosphatase (AP) is found in the epithelial cells of the proximal tubule [14]. As such, once serum creatinine, cystatin C and urinary enzymes are determined, results that would possibly quantify perioperative injury to the kidneys may be obtained.

Thus, the aim of this clinical prospective trial was to assess the effects of two analgesia regimens on post-operative renal function in patients submitted to general anesthesia for laparoscopic cholecystectomy.

2. METHODS

This was a randomized, placebo-controlled, double-blind trial. After Institutional Review Board approval, written informed consent was obtained from a total of 126 patients scheduled for general anesthesia for elective laparoscopic cholecystectomy with CO2 pneumoperitoneum at 13 mmHg for chronic cholecystitis due to cholelithiasis. Patients older than 60 years, allergic to NSAIDs or opioids, with an ASA physical status of more than III, plasma creatinine higher than 1.5 mg/dl or heart failure, and users of nephrotoxic drugs were excluded. Oral 15 mg midazolam was given as pre-medication to all patients, one hour before anesthesia. Patients were included in one of two groups: Dipyrone group—received placebo (saline) intravenously (iv) at the time of pre-medication, and 100 mg tramadol with 2 g dipyrone, iv, approximately 30 min before the end of anesthesia for analgesia; Ketorolac group—received 30 mg ketorolac, iv, at the time of pre-medication, and 100 mg tramadol with 30 mg ketorolac, iv, approximately 30 min before the end of anesthesia for analgesia. The placebo and ketorolac solutions were administered by a nurse, who prepared them in an identical volume (10 ml). The same nurse prepared the drugs for postoperative analgesia, so that the double-blind condition of the study was maintained.

In the operating theater, all patients were monitored with electrocardiography, pulse oxymeter and non-invasive arterial pressure measurement. All patients were given 10 ml/kg/h Ringer lactate solution. At this time point (T1), 20 ml of blood were collected for the laboratory assessment of cystatin C, by the immunonephelometric method using Dade Behring® reagents and calibrators (N Latex Cystatin C, Dade Behring, Deerfield, USA), urea and creatinine (dry-chemical method), and albumin by protein electrophoresis. Additionally, 80 ml of urine (after bladder catheterization) were collected to dose AP, γ-GT, and creatinine, by the Vitros 950—Johnson & Johnson® (USA) automation system. Urinary creatinine concentrations in mg/dl were multiplied by 0.0884 for conversion to mmol/l, and used to eliminate the effect of urinary dilution: AP/creatinine (U/mmol); γ-GT/creatinine (U/mmol); AP × γ-GT/creatinine (U/mmol).

Twenty four hours after the end of anesthesia and surgery (time point T2), 20 ml of blood and 80 ml of urine were once more collected, and the same laboratory assays were repeated.

2.1. Anesthesia Procedures

Anesthesia was induced with intravenous 0.5 μg/kg/min remifentanil, 2 mg/kg propofol, and 0.6 mg/kg rocuronium. After tracheal intubation to perform general anesthesia, intermittent positive pressure ventilation was continued, and end-tidal carbon dioxide pressure was monitored to remain around 33 mmHg. Anesthesia was maintained with 0.25 μg/kg/min remifentanil, sevoflurane adjusted according to hemodynamic parameters, 4
liters of fresh gas comprising N₂O in 50% of O₂, controlled breathing and rebreathing with a semiclosed system.

Analgesia in patients from both the Dipyrone and the Ketorolac groups was assessed by the Verbal Numerical Scale (VNS) at admission to the post-anesthesia care unit (PACU), and at every 15 minutes until discharge, at least two hours after admission to the PACU. According to instructions received before anesthesia and surgery, patients rated pain on a zero-ten scale where: zero = absence of pain, one (1) = minimum existing pain, and 10 = the worst pain imaginable. In the PACU, when values were above three in the VNS, 1mg morphine hydrochloride was administered, iv, every 10 minutes until pain cessation or VNS = 3. Level of sedation (awake and uncooperative) and quantity of morphine used were also assessed in the PACU.

GFR was estimated by the following formulas: GFR-Larsson (ml/min) [15,16] = 77.24 × [cystatin C⁻¹.2623 (mg/l)]; GFR-MDRD (“Modification of Diet in Renal Disease”) (ml/min/1.73m²) [17] = 170 × (creatinine)⁻⁰.⁹⁹⁹ × (age)⁻⁰.¹⁷⁶ × [0.762 if female] × [1.18 if black] × (urea)⁰.¹⁷ × (albumin)⁰.³¹⁸ and GFR-CG (ml/min) [18] = (140 – age) × weight/serum creatinine x 72 × [0.85 if female].

2.2. Statistical Analysis

The exact Fisher test was used to study the association between group and gender. The Student t test was used for comparisons between groups regarding age, pre- and postoperative cystatin C level (Δ cystatin C), and the amount of morphine used in the PACU. Profile analysis was used to study the effect of group, time and time × group interactions. Correlations between variables were analyzed by Pearson’s correlation coefficient. Statistical significance was set at p < 0.05.

3. RESULTS

Duration of anesthesia was 70 min ± 10 in the Dipyrone group, and 68 min ± 13 in the Ketorolac group (p = 0.42). Age was 40.9 years ± 12.1 in the Dipyrone group, and 40.2 years ± 11.5 in the Ketorolac group (p = 0.75). In the Dipyrone and Ketorolac groups, females represented 73% (46) and 82.5% (52) of the patients, respectively (p = 0.28). Weight was 71.5 kg ± 13.5 in the Dipyrone group, and 73.6 kg ± 14.9 in the Ketorolac group (p = 0.31). It can be said that the groups were homogeneous (Table 1).

Cystatin C values did not differ between groups (p = 0.30), and time points (p = 0.09), and there was no time points × groups interaction (p = 0.44) (Table 1). Serum creatinine values were not different between groups (p = 0.62), nor was there time points × groups interaction (p = 0.10). However, there was a difference between time points (p = 0.00001) (Table 1). Plasma albumin presented the same profile with no difference between groups (p = 0.42), without time points × groups interaction (p = 0.27), but showing a difference between time points (p = 0.0005) (Table 1).

The GFR-Larsson was not different between groups (p = 0.33), and time points (p = 0.07), and there was no time points × groups interaction (p = 0.66) (Table 2). GFR-CG was not different between groups (p = 0.79), and did not exhibit time points × groups interaction (p = 0.55). However, it was different between time points (p = 0.001) (Table 2). GFR-MDRD was not different between groups (p = 0.72), and did not exhibit time points × groups interaction (p = 0.58), but it differed between time points (p = 0.003) (Table 2). A significant correlation was observed only between GFR-MDRD and GFR-CG values at T1 (r = 0.48 and p = 0.000) and T2 (r = 0.36 and p = 0.000).

AP results significantly differed between groups (p = 0.02) and time points (p = 0.03), and showed time points × groups interaction (p = 0.001). Thus, Dipyrone group > Ketorolac group and T1 < T2 (Table 2). γ-GT presented a statistically significant difference between groups (p = 0.001), and time points × groups interaction (p = 0.00002), with no difference between time points (p = 0.07). The product of the two enzymes significantly differed between groups (p = 0.005) and time points (p = 0.008), and showed time points × groups interaction (p = 0.0002) (Table 2).

Table 1. Clinical data of study group patients (Means ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dipyrone group (n = 63)</th>
<th>Ketorolac group (n = 63)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.9 ± 12.1</td>
<td>40.2 ± 11.5</td>
<td>0.75</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.5 ±13.5</td>
<td>73.6 ± 14.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Gender F:M</td>
<td>46:17</td>
<td>52:11</td>
<td>0.28</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>70 ± 10</td>
<td>68 ± 13</td>
<td>0.42</td>
</tr>
<tr>
<td>Plasma cystatin C (mg/l)</td>
<td>T1 0.83 ± 0.19</td>
<td>0.78 ± 0.18</td>
<td>*0.31</td>
</tr>
<tr>
<td></td>
<td>T2 0.84 ± 0.18</td>
<td>0.81 ± 0.17</td>
<td>*0.24</td>
</tr>
<tr>
<td>Blood creatinine (mg/dl)</td>
<td>T1 0.78 ± 0.14</td>
<td>0.77 ± 0.16</td>
<td>*0.62</td>
</tr>
<tr>
<td></td>
<td>T2 0.70 ± 0.16</td>
<td>0.73 ± 0.19</td>
<td>*0.0001</td>
</tr>
<tr>
<td>Plasma albumin (g/dl)</td>
<td>T1 4.1 ± 0.7</td>
<td>4.1 ± 0.5</td>
<td>*0.42</td>
</tr>
<tr>
<td></td>
<td>T2 3.3 ± 0.7</td>
<td>3.7 ± 2.5</td>
<td>*0.0005</td>
</tr>
<tr>
<td>Δ cystatin C (mg/ml)</td>
<td>0.0017 ± 0.14</td>
<td>0.0030 ± 0.15</td>
<td>*0.23</td>
</tr>
</tbody>
</table>

* = p between Dipyrone and Ketorolac groups; * = p between time point 1 (T1—at the arriving in operating theater) and time point 2 (T2—24 h after the end of anesthesia and surgery).
However, did not reach statistical significance (the Ketorolac groups, respectively). Such difference, (0.95 mg ± 1.55 and 0.71 mg ± 1.21 for the Dipyrone and dose needed for pain control differed between groups received morphine in the postoperative period and the total adverse effects of prolonged (4 hours) CO₂ pneumoperitoneum [19,20]. In a porcine model, volume expansion renal plasma flow, GFR, sodium excretion and urine organs such as the kidney. During pneumoperitoneum at abdominal pressure may lead to restrictive flow to vital organs in the surgery theater (T1) and after 24 hours of anesthesia and surgery (T2) (Means ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dipyran group (n = 63)</th>
<th>Ketorolac group (n = 63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR-Larsson (ml/min)</td>
<td>T1: 61.5 ± 19.4</td>
<td>T2: 60.2 ± 17.4</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>T1: 62.0 ± 17.4</td>
<td>T2: 61.6 ± 17.0</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>T1: 114.6 ± 29.5</td>
<td>T2: 119.1 ± 29.8</td>
<td>0.79</td>
</tr>
<tr>
<td>GFR-CG (ml/min)</td>
<td>T1: 127.7 ± 38.2</td>
<td>T2: 126.1 ± 32.7</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>T1: 94.2 ± 32.6</td>
<td>T2: 93.7 ± 26.5</td>
<td>0.72</td>
</tr>
<tr>
<td>GFR-MDRD (ml/min/1.73 m²)</td>
<td>T1: 105.5 ± 42.8</td>
<td>T2: 101.6 ± 44.8</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>T1: 2.7 ± 1.1</td>
<td>T2: 2.0 ± 0.3</td>
<td>0.02</td>
</tr>
<tr>
<td>AP/UCr (U/mmol)</td>
<td>T1: 3.5 ± 1.6</td>
<td>T2: 3.5 ± 0.8</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>T1: 4.1 ± 2.0</td>
<td>T2: 5.0 ± 1.2</td>
<td>0.001</td>
</tr>
<tr>
<td>γ-GT/UCr (U/mmol)</td>
<td>T1: 3.3 ± 1.8</td>
<td>T2: 5.5 ± 2.5</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>T1: 134.2 ± 68.4</td>
<td>T2: 86.3 ± 22.0</td>
<td>0.005</td>
</tr>
<tr>
<td>AP x γ-GT/UCr (U/mmol)</td>
<td>T1: 85.1 ± 45.8</td>
<td>T2: 167.0 ± 83.8</td>
<td>0.008</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; AP = alkaline phosphatase; γ-GT = γ-glutamyltransferase; UCr=urinary creatinine; * = p between Dipyran and Ketorolac groups; † = p between time points T1 and T2.

All patients were awake at PACU admission. VNS scores gradually decreased with time for all patients, but groups differed at PACU discharge, when the Dipyran group mean score (2.0 ± 1.7) was higher than that of the Ketorolac group (1.6 ± 1.6) (p = 0.04). All patients received morphine in the postoperative period and the total dose needed for pain control differed between groups (0.95 mg ± 1.55 and 0.71 mg ± 1.21 for the Dipyran and the Ketorolac groups, respectively). Such difference, however, did not reach statistical significance (p = 0.34).

4. DISCUSSION

Hypovolemia in combination with high intraabdominal pressure may lead to restrictive flow to vital organs such as the kidney. During pneumoperitoneum at 12 mmHg, compressive effects on the renal parenchyma, renal vessels and inferior vena cava reduce effective renal plasma flow, GFR, sodium excretion and urine output [19,20]. In a porcine model, volume expansion with 15 ml/kg/h isotonic solution could reverse the adverse effects of prolonged (4 hours) CO₂ pneumoperitoneum (15 mmHg) on renal blood flow and urine output [1]. When pneumoperitoneum is associated with NSAID administration and pre-existing kidney disease, acute renal failure may occur. Nevertheless, the use of NSAID can be safe in well hydrated patients without previous renal dysfunction [21], while in patients with normal preoperative renal function it may cause a transitory decrease of 16 ml/min in GFR in the early postoperative period [22]. The patients included in this study presented normal plasma creatinine and were submitted to 13 mmHg pneumoperitoneum, but they were well hydrated during anesthesia.

GFR needs to be reduced 75% before serum creatinine reaches abnormal levels [23] and blood creatinine concentration is affected by other factors that do not depend upon renal function or injuries [24]. In this study, serum creatinine decreased in both groups in the postoperative period, probably due to hemodilution caused by intraoperative fluid loading and release of antidiuretic hormone, considered as a stress hormone that acts to maintain homeostasis [25-27]. According to the Cockcroft & Gault formula [18], that estimates creatinine clearance, a postoperative GFR increase might have occurred in both groups as creatinine concentrations decreased. Did kidney function improve postoperatively in these patients? Albumin concentrations also decreased in both groups over the same period, and this speaks in favor of hemodilution in the postoperative period [28], holding it responsible for the decrease in creatinine and increase in its clearance. Since there was a positive correlation between the Cockcroft & Gault method and the MDRD method, that also uses serum creatinine—and albumin—results, the GFR values obtained by both methods may be overestimated. Thus, no change in the concentration of the endogenous marker could be observed unless an important renal injury exceeding the dilution factor had occurred.

No significant difference was found between preoperative and postoperative cystatin C in both groups. If there had been hemodilution and no decrease in cystatin C values, can one infer that these values would have indeed increased? Because cystatin C changes in these patients before creatinine over the postoperative period, would then a decrease in GFR have occurred? After filtration by the glomerulus, cystatin C is reabsorbed and catabolized (without secretion) by tubular epithelial cells, and only insignificant amounts are excreted in the urine [29]. As a consequence, although cystatin C is cleared by the kidneys, its urinary clearance is not routinely measured. Cystatin C would be a better marker of renal function than plasma creatinine [30,31]—its production seems to be less variable between patients than that of creatinine. However, there is evidence that serum cystatin C levels are influenced by corticoid use, and by thyroid function. Cystatin C levels appear to be related to age, gender, weight, height, tobacco smoking status, and C reactive protein concentration [32,33]. A cystatin C (between pre and postoperative values of each group) showed no significant difference. However, it was greater in the group that received ketorolac. Further research is
needed to find out whether this is clinically relevant.

In this study, the endogenous biomarkers of renal injury AP and γ-GT were dosed in urine. The increased secretion of both markers, that takes place before serum creatinine increases, indicates injury in the brush border membrane and loss of the microvilli structure. In rats submitted to an excessive dose of paracetamol (leading to acute proximal tubular injury), the urinary levels of these enzymes significantly increased in the first 24 hours, and returned to nearly baseline values after 48 - 72 hours, while GFR drastically decreased [34].

Our results show that urinary AP increased 24 h after surgery in both groups, indicating alteration in the tubular cells after surgery, apparently not related to ketorolac use. In the group that did not receive NSAID, AP values were higher at both time points studied. The concentration of γ-GT did not significantly change in the postoperative period in both groups, and in contrast with AP, it remained higher in the Ketorolac group. The product of both urinary enzymes showed a different profile in both groups and time points. In the Dipyrone group, the product was significantly higher preoperatively, but it decreased in the postoperative period. In patients receiving ketorolac, urinary enzyme product was significantly increased postoperatively. Whether such increase indicates some degree of injury at the brush border membrane of the tubular cell is not clear. Further studies are necessary to substantiate and better explain these results.

The cross-talk mechanism involving the afferent and efferent arterioles and the renal tubules has been demonstrated. Such relation would be more intense than expected by the anatomical contact between these structures, and has been known for a long time as the juxtaglomerular apparatus. Thus, decreased stress and stress hormones may indirectly influence the tubules by acting on these renal capillaries [36].

Ketorolac given as a pre-medication drug (0.5 mg/kg) in gynecological laparoscopy has been reported to influence the response of white blood cells, which is usually affected by surgical stress [37]. Administered intravenously, 15 mg ketorolac followed by 7.5 mg/h, in elective cesarean section, eased hemodynamic response to stress of tracheal intubation, improving the quality of analgesia and determining lower concentrations of plasma cortisol [38]. Ketorolac reaches maximum plasma concentration in 45 minutes and analgesic peak in one or two hours with an increased peak in aged patients with impaired renal function. In a study of 40 dogs submitted to hysterectomy and oophorectomy under general anesthesia, ketorolac was administered as one of the analgesics for treatment of postoperative pain (0.5 mg/kg). The analysis of serum creatinine and urea and renal function biomarkers such as γ-GT and AP showed that ketorolac is safe for this purpose [39].

In this study, good results were achieved using analgesia for pain control in both groups. According to VNS, only a small amount of rescue analgesia (morphine) was needed. Treatment with ketorolac as a premedication may ease renal response to preoperative stress. Additionally, low-dose ketorolac instillation into wounds has been demonstrated to modulate local inflammatory events, decrease postoperative pain, and reduce opioid consumption, suggesting that the administration of NSAIDs into surgical wounds may be an analgesic alternative to higher systemic dosing of NSAIDs [40].

In conclusion, both analgesia regimens used in this study that combined tramadol with either dipyrone or ketorolac, in well hydrated patients submitted to laparoscopic cholecystectomy, showed similar results in the PACU. Postoperatively, the effect on GFR might have been masked by hemodilution, but there was a discreet increase in the release of renal tubular enzymes when ketorolac was used, a response that requires further clarification.

5. ACKNOWLEDGEMENTS

Grant 07/51101-0—São Paulo Research Foundation (FAPESP); TP Medeiros was granted a scholarship from CAPES.

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