Post operative pain: analgesic combinations and adverse effects*

DOR PÓS-OPERATÓRIA: COMBINAÇÕES ANALGÉSICAS E EVENTOS ADVERSOS

DOLOR POSTOPERATORIO: COMBINACIONES ANALGÉSICAS Y EVENTOS ADVERSOS

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ABSTRACT

The control f the pains and its adverse affects are in the focus of health professionals and institutional managers in order to optimize clinical outcomes. The objectives of this study were to analyze the prevalence of medicine combination and interaction and to verify the association of this with the observed adverse effects. It was a descriptive, exploratory and retrospective study. The sample was composed by 260 patient data submitted to hemorrhoidectomy, up to 60 years old, healthy. Results showed that the mostly used medicine associations were dipyrone sodium and omeprazole (33.7%), dypirone sodium and ketoprofen (23.6%) and cetoprofen and lactulose (22.8%). It was observed that ketoprofen + omeprazole (p=0.001) and ketoprofen + lactulose (p=0.03) were significantly associated with bleeding. It was observed that, excepting ketoprofen, the other medicine association identified in the study showed to be safe to be used in the post surgical period.

KEY WORDS

Pain, postoperative.
Drug interactions.
Analgesics.

RESUMO

O controle da dor e seus eventos adversos são focos de profissionais e gestores das instituições de saúde para obtenção de desfechos assistenciais. O estudo teve como objetivos analisar a prevalência de combinações e interações medicamentosas da terapia analgésica e verificar a associação dessa com os eventos adversos conferidos. Trata-se de estudo descritivo, exploratório e retrospectivo. A amostra foi composta por 260 prontuários de pacientes submetidos a hemorroidectomia, com idade de até 60 anos hígidos. Os resultados mostraram que as associações medicamentosas mais utilizadas foram a dipirona+omeprazol (33,7%), dipirona+cetoprofeno (23,6%) e cetoprofeno+lactulose (22,8%). Observou-se que cetoprofeno+ omeprazol (p=0,001) e cetoprofeno+ lactulose (p=0,03) estiveram significativamente relacionados com sangramento. Concluiu-se que, com exceção do cetoprofeno, as outras associações medicamentosas identificadas no estudo se mostraram seguras para serem utilizadas no período pós operatório.

DESCRITORES

Dor pós-operatória.
Interações de medicamentos.
Analgésicos

RESUMEN

El control del dolor y sus eventos adversos se constituyen en el foco de los profesionales y gestores de las instituciones de salud para la obtención de resultados asistenciales. El estudio tuvo como objetivos analizar la prevalencia de combinaciones y interacciones medicamentosas de la terapia analgésica y verificar la asociación de esta con los eventos adversos conferidos. Estudio descriptivo, exploratorio y retrospectivo. La muestra fue compuesta por 260 historias clinicas de pacientes sometidos a hemorroidectomia hasta los 60 años de edad, sanos. Los resultados mostraron que las asociaciones medicamentosas más utilizadas fueron la dipirona y omeprazol (33,7%), dipirona y cetoprofeno (23,6%) y cetoprofeno y lactulosa (22,8%). Se observó que el cetoprofeno+omeprazol (p=0,001), cetoprofeno+ lactulosa (p=0,03) estuvieron significativamente relacionados con el sangramiento. Se concluyó que, con excepción del cetoprofeno, las otras asociaciones medicamentosas identificadas en el estudio se mostraron seguras para ser utilizadas durante el período postoperatorio.

DESCRIPTORES

Dolor postoperatorio.
Interacciones de drogas.
Analgésicos.

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INTRODUCTION

Postoperative pain is the most prevalent type of acute pain experienced by thousands of people in the world, occurring at the rates of 29.7% and 10.9% for moderate or intense types, respectively. It is an autonomic, psychological and behavioral response that results from the complex physiological reaction to tissue lesion, causing a sensitive and emotional experience that is unpleasant and undesired[1-2].

The somatic and psychic expression of pain can be directly or indirectly associated with the increase in morbimortality and to the length of stay, with consequent social and economic effects. The persistence of pain, especially when sharp and prolonged, tends to increase the occurrence of adverse events, causing undesired clinical outcomes[3].

Clinical and experimental studies have addressed issues regarding the epidemiology of pain, both acute and chronic, but there is still much to be investigated in the search for safe and effective protocols for pain management.

Many of these studies derive from animal experiments, as they present behavioral and physiological responses equal to that of humans, stressing that animals should not receive a painful stimulus greater than what is bearable in humans and that it can be interrupted at any time if considered necessary. Some results in this area reiterate basic concepts about the reaction to pain. It was observed that variables regarding care and individual motivation are more precisely determinants of the intensity of pain than of changes in sensorial perception. Therefore, there have been improvements to mechanisms that measure the intensity of pain, which today represent safe and effective clinical tools, considering they have become closer to the individualization setting. Nevertheless, other measures for controlling the adverse effects associated with analgesic combination should receive special attention[4].

Effective pain management is essential when providing care for surgical patients, and the pharmacological therapy aims at minimizing discomfort, prevent deleterious effects, facilitate the process of recuperation and make the treatment economically feasible[3]. Achieving these objectives depends on the form that the analgesic therapy occurs especially regarding the combination of medications. This measure is a current concern for professionals involved in health care and for institutional administrators who aim at achieving excellent outcomes.

In Brazil, the interest of institutions in receiving accreditation and certification for the quality of hospital services by programs as those proposed by the National Accreditation Organization (NAO) and the *Joint Commission on the Accreditation of Healthcare Organizations* – JCAHO has proven the importance of safety and quality in the care delivered to patients, including those involving the effective pain management[5].

In the United States, professionals working at hospitals are concerned with the evaluation of the outcomes and with the occurrence of adverse events to analgesic therapies, because pain is one of the most common symptoms and an indicator of quality[5].

The safety and quality of the pain management process are directly related with factors such as the patient's characteristics, the appropriate indication of drug use, correct administration, the careful selection of the drugs and evaluation of their adverse events, especially by the nursing team, which is responsible for the full-time monitoring of patients.

According to recent terminology, adverse events are understood as those that harm the patient, and are caused by using a medication, or interrupting its use when necessary. These events can be avoidable, as in cases of medication errors. Others are unavoidable, such as cases of adverse drug reactions (ADR), which represent any harmful or unwanted effect that appears after the correct administration of the medication in therapeutic doses, with the possibility of causing harm[6].

Effective pain management is essential when providing care for surgical patients, and the pharmacological therapy aims at minimizing discomfort, prevent deleterious effects, facilitate the process of recuperation and make the treatment economically feasible.

Balanced analgesia, whose principle includes the use of a combination of analgesic drugs with the purpose of improving pain management, reducing doses and ADRs, does not always produce desired outcomes, and can cause adverse events, which in this context are understood as the precipitation of ADR or drug interactions (DI). These events can be considered an important health issue, because besides causing an impact on patient safety, they imply higher costs. However, it is common for these occurrences to be inappropriately identified and reported by health professionals, either because of their lack of knowledge or misinterpretation of the patients' signs and symptoms and complaints.

Considering that studies on this matter remain incipient, the undesired signs and symptoms, which are mainly identified by the nursing team, represent important indicators of the responses to medications. Therefore, the present study was performed with the purpose to analyze the profile of the analgesic therapy in the postoperative (PO) period regarding the prevalence of combinations and potential DI, and verify the associations between signs and symptoms that indicate adverse events in drug combinations.

METHOD

This is a descriptive, exploratory and retrospective study. The population consisted of 260 medical records of

patients submitted to hemorrhoidectomy between January and December 2004 at a private general hospital in the city of São Paulo.

The convenience sample consisted of adults with 60 years of age or less, healthy according to the physical evaluation established by the *American Society of Anesthesiologists* – ASA at the levels I and II, submitted to elective closed hemorrhoidectomy and by the same coloproctology team.

Data collection was performed after being approved by the Ethics Committee at the Institution, using a form containing patient identification information (age, gender, use of medications at home, smoking and drinking habits, and preexisting diseases), pharmacological treatment (medication, dose, administration route and frequency) and the signs and symptoms reported in the nursing notes and on the medical evolution sheet.

The drug combinations, when reported, were analyzed in terms of the presence or absence of DI, according to specialized literature[7-8]. The potential ADRs were identified according to the *Drug Information Handbook International*[9]. Signs and symptoms were analyzed using the medical records of patients who were in the first PO day (1PO), exclusively. This way, in this part of the analysis the population consisted of 239 medical records. Patients in immediate PO (POI) were excluded from this study to avoid any interference from the anesthetics in the patients' signs and symptoms.

Data analysis was performed using the program SPSS 12.0, and the statistical tests used were the Kolmogorov-Smirnof and *Pearson's* Chi-square at a 5% significance level.

RESULTS

It was verified there is a predominance of female patients (54.5%), with an average age of 44.4 years, who used medications at home (54.1%), did not drink or smoke (65.4%), did not have any preexisting comorbidity (64.2%), classified as ASA I (73.2%), used pre-anesthetic (96.9%) and received general anesthesia (99.2%).

During the POI and 1PO periods, respectively, an average of 4.08 and 3.78 medications was administered per day, in addition to 2.41 analgesics. There were 1.43 signs and symptoms during POI per patient.

It was observed that pain (54.4%) and bleeding (48.1%) were the most prevalent signs and symptoms among patients during 1PO (Table 1).

During POI and 1PO, the most prescribed medications were: dipyrone (79.6%), omeprazole (66.5%) and ketoprofen (66.1%). It was observed that use of dipyrone (85.4%) and ketoprofen (74.1%) was maintained during 1PO.

Table 1 - Patient distribution according to the occurrence of signs and symptoms - São Paulo - 2004

Signs and symptoms	Patients	
	N	%
Pain	129	54.0
Bleeding	115	48.1
Abdominal pain	75	31.4
Nausea	15	6.3
Vomiting	07	2.9

Eighteen drug combinations were identified. Most included dipyrone + omeprazole (33.7%) and dipyrone + ketoprofen (23.6%), (Table 2).

Table 2 - Patient distribution according to drug combinations existing in the first postoperative period - São Paulo - 2004

Drug combination	Total	
	N	%
Dipyrone + Omeprazole	83	33.7
Dipyrone + Ketoprofen	58	23.6
Ketoprofen + Lactulose	56	22.8
Dipyrone + Cefoxitin	33	13.4
Ketoprofen + Omeprazole	32	13.1
Dipyrone + Lactulose	24	9.8
Rofecoxib + Lactulose	16	6.5
Dipyrone + Rofecoxib	8	3.1
Ketoprofen + Ranitidine	7	2.8
Meperidine + Lactulose	7	2.8
Oxycodone + Lactulose	5	2.0
Ketoprofen+ Meperidine	4	1.6
Lactulose + Omeprazole	4	1.6
Dipyrone + Bromopride	3	1.2
(Adiphenine+Dipyrone+Promethazine) + Omeprazole	3	1.2
Meperidine + Omeprazole	2	0.8
Cefoxitin + Omeprazole	2	0.8
Ketoprofen + Oxycodone	2	0.8

These combinations were analyzed for the existence of DI among their agents. Only one DI was found between ketoprofen + ranitidine of low severity and delayed onset.

Table 3 lists signs and symptoms and the combination between analgesics and adjuvants, and shows there was a significant association between the symptom of pain and use of the combinations dipyrone+omeprazole (p = 0.01) and lactulose+ketoprofen (p = 0.01). There was a statistically significant association between the combination of ketoprofen+omeprazole and bleeding (p=0.001); and lactulose+ketoprofen and bleeding (p=0.03).

Table 3 - Patient distribution according to signs and symptoms and drug combinations - São Paulo - 2004

Signs and Symptoms	Ketoprofen + Dipyrone			Omeprazole + Dipyrone			Lactulose + Dipyrone			Omeprazole + Ketoprofen			Lactulose + Ketoprofen		
	No	Yes	*p*	No	Yes	*p*	No	Yes	*p*	No	Yes	*p*	No	Yes	*p*
Pain															
No	35	67	0.10	58	47	0.01	45	44	0.26	41	51	0.07	44	59	0.01
Yes	24	90		47	74		50	67		39	81		32	90	
Bleeding															
No	40	73	0.30	52	63	0.70	52	51	0.20	52	53	0.001	46	68	0.03
Yes	24	84		53	58		43	60		28	79		30	81	
Nausea															
No	62	145	0.21	98	114	0.80	88	105	0.56	75	122	0.71	73	137	0.24
Yes	2	12		7	7		7	6		5	10		3	12	
Vomiting															
No	61	153	0.41	103	116	0.45	90	109	0.25	77	128	1.00	75	142	0.22
Yes	3	4		2	5		5	2		3	4		1	7	
Abdominal pain															
No	45	110	0.97	73	82	0.77	68	74	0.44	57	89	0.56	54	101	0.61
Yes	19	46		32	39		27	37		23	43		22	48	

Patients who used NSAI+AO had a significantly greater number of cases of bleeding compared to the group that used NSAI+NSAI (p=0.001) (Table 4).

Table 4 - Patient distribution according to signs and symptoms and use of nonsteroidal anti-inflammatory drug combinations (NSAI) and between NSAI and opioid analgesics (OA) - São Paulo - 2004

Signs and symptoms	NSAI+NSAI	NSAI+AO	p
Pain			
No	72	38	0.10
Yes	71	58	
Bleeding			
No	96	28	0.001
Yes	47	68	
Nausea			
No	136	88	0.28
Yes	07	08	
Vomiting			
No	138	93	1.0
Yes	04	03	
Abdominal pain			
No	104	60	0.09
Yes	39	36	

NSAI=nonsteroidal anti-inflammatory drug, OA = opioid analgesic

DISCUSSION

The present study found that the most used drug classes were analgesics and agents that can compromise the digestive system, both with the purpose of reducing discomfort and relieving pain in patient submitted to hemorrhoidectomy. The intensity of pain among these patients, usually moderate to intense, was often related to the pattern of bowel functioning, thus requiring important adjuvant measures, as the use of laxatives[3,10].

As for analgesics, it was found that dipyrone and ketoprofen were the most used. Dipyrone is currently considered one of the main analgesics, whose clinical efficacy in postoperative pain has been reported in several studies, especially as an adjuvant in surgeries such as hemorrhoidectomy[3,10-13]. Studies show that high doses of dipyrone are similar to the administration of OA such as tramadol and meperidine[14]. Ketoprofen is also often stated for pain management in PO of hemorrhoidectomy patients[3].

NSAI are the most common drugs used for pain management in PO. In the United States NSAI represent over 111 million prescriptions. They are strong analgesics that can be used in single- and multi-modal approaches, including recovering analgesia. The preference of this class of medications is due to fact that they do not induce sedation or respiratory depression and can significantly reduce the need for OA. In addition, patients treated with NSAI demonstrate a greater reduction in the intensity of pain and need little additional analgesia[14-15]. Clearly, undesirable effects such as gastric bleeding and acute renal lesion should not be disregarded when indicating these agents.

In terms of drug combinations, it was found that the combination between analgesics with the same action mechanism, i.e., inhibition of cyclooxygenases (COX) whether it is 1, 2 or 3, (dipyrone+ketoprofen; dipyrone +rofecoxibe), as verified in the present study, can increase the occurrence of ADR such as abdominal pain and the risk of bleeding[16-17]. Nevertheless, although there was a greater number of abdominal pain cases among patients who used NSAI, no statistically significant difference was found between those who received the NSAI+AO combination.

More than half of patients (54.0%) reported the occurrence of pain, which can be associated with the low frequency in the use of multi-modal approaches that include

NSAI+AO. In addition, prevalent combinations as the ones identified (NSAI+NSAI) do not improve the additional analgesic effect, since these pharmaceuticals present ceiling effect[3,9].

About one-third of the population (31.4%) reported abdominal pain, despite the co-prescription of gastric secretion inhibitors. This frequency can be considered relatively high if compared to other studies that evaluated ulceration and bleeding after chronic use of NSAI[16-17]. On the other hand, the low frequency of other gastrointestinal system symptoms such as nausea and vomiting occurred due to the restricted use of OA . It is a fact that, regardless of the frequency, the occurrence of any of these signs or symptoms can increase the length of stay and, indirectly, expose patients to the risk of adverse events such as ADRs and DIs, especially in situations involving the existence of comorbidities and the use of chronic medication.

The identified combinations could, initially, affect the pattern of agent absorption, considering that most combined NSAI and anti-ulcer drugs. NSAI are weak acids, which in contact with an alkaline pH (provided by the use of H_2 antagonists and proton pump blockers) become more ionized, which makes it more difficult for the drug to cross the plasma membrane, delaying the absorption of NSAI. Nevertheless, literature shows that ketoprofen was the only NSAI involved in DI, perhaps due to the high bond to plasma proteins (99%), which combined with ranitidine. This DI, whose mechanism is unknown, is classified as being of low severity, i.e., the interaction presents limited effects that usually do not require treatment[8-9].

A significant association was observed between the occurrence of pain and the use of the combinations dipyrone +omeprazole (p=0.01) and ketoprofen+lactulose (p=0.01). This fact can be explained by the alteration of the gastrointestinal tract pH, with a consequent delay in the absorption of NSAI and in the analgesic effect. In contrast, there was no association between incision bleeding and the use of the ketoprofen+dipyrone combination, though it could be expected, because both agents, at higher and lower levels, can cause blood dyscrasias and increase the risk for ADR, when in combination.

Lesion bleeding was associated with using ketoprofen +omeprazole (p=0.001) and ketoprofen+lactulose (p=0.03). It is likely that ketoprofen, in both cases, increased the risk for hemorrhage due to the inhibition of platelet function, thus increasing the occurrence of surgical wound bleeding[9]. Furthermore, in cases of the ketoprofen+lactulose combination, bleeding may occur due to straining during defecation, which is stimulated by the use of laxatives.

In regard to postoperative pain management, the fact that the most commonly used analgesics (NSAI) do not present DI, apart from ketoprofen, is very positive because these agents are frequently combined to other medications during the PO period. However, ADR tracking, especially for NSAI, should be systematically monitored by the health team because the drugs involved in the undesired occurrences found in this study belonged to this drug class.

The prevalent signs and symptoms (pain, bleeding and abdominal pain) associated with drug combinations can be indicative of adverse events, despite the fact that the analyzed sample was small and restricted to a particular surgical procedure, and the fact it is a retrospective study, which limited the researchers to working with previously registered information. In this sense, it is suggested that further prospective studies be performed to refute or corroborate the findings of the present study and increment information to improve patient care quality regarding postoperative pain management.

CONCLUSION

The analysis of the prevalence of drug combinations and potential DI existing in the analgesic therapy during the PO period, and of associations between signs and symptoms indicative of adverse events with the drug combinations permitted to draw the following conclusions: pain (54.4%) and bleeding (48.1%) were the signs and symptoms indicative of prevalent adverse events among patients during 1PO; 46.8% of patients received drug combinations with NSAI (dipyrone or ketoprofen) and proton pump blockers (omeprazole); only one low severity delayed onset DI was found for ketoprofen+ranitidine, used by 2.8% of the sample; a significant association was found between the presence of pain and the use of dipyrone +omeprazole (p=0.01) and lactulose+ketoprofen (p=0.01); and between the occurrence of bleeding and the use of ketoprofen+omerazol (p=0.001) and lactulose+ketoprofen (p=0.03).

In nursing, although signs and symptoms are considered intermediate outcomes for health care evaluation, they are essential in postoperative pain management, because they can help “measure” the success or failure of commonly used drug combinations. Therefore, a systematic evaluation of patients submitted to analgesic therapy could help the medical team to adjust the patient’s therapeutic regimen, support the proposition of preventive interventions, with the purpose of avoiding adversities, and contribute with the service of pharmacovigilance in terms of reporting adverse events.

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