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Clinical efficiency and safety of tramadol and low-dose morphine to manage pain syndromes in children following chemotherapy and hematopoietic stem cell transplantation

Ekaterina V. Goncharova [1,2], Inga E. Zavodova [1], Nikita P. Volkov [1], Olga A. Ivanova [1], Maxim A. Kucher [1], Alexey Y. Sokolov [2,3], Maxim P. Bogomolny [1], Gleb E. Ulrikh [4], Ludmila S. Zubarovskaya [1], Boris V. Afanasyev [1]

[1] RM Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantation, Pavlov University, St. Petersburg, Russia
[2] Department of Neuropharmacology, Valdman Institute of Pharmacology, Pavlov University, St. Petersburg, Russia
[3] Pavlov Institute of Physiology of the Russian Academy of Sciences, St. Petersburg, Russia
[4] Department of Anesthesiology and Pediatric Intensive Care, Saint Petersburg State Pediatric Medical University, St. Petersburg, Russia

Dr. Ekaterina V. Goncharova, RM Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantation, Pavlov University, L.Tolstoy St. 6-8, 197022, St. Petersburg, Russia
Phone: +7 (911) 087 8976
E-mail: ek.v.goncharova@gmail.com

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Summary

A sufficient subgroup of patients encounters pain syndrome in the course of cytostatic chemotherapy (ChT), either with or without hematopoietic stem cell transplantation (HSCT). Over this time period, severe thrombocytopenia and leucopenia may develop, thus limiting the opportunities for non-steroidal anti-inflammatory drugs (NSAID). As recommended by WHO, administration of strong opioids to children is possible in moderate pain and inefficiency of NSAIDs. In this case, second step of the pain relief ladder is absent, i.e., codeine application. However, the recommendations do not exclude usage of tramadol, which is widely applied in pediatrics. Our aim was to evaluate relative safety and efficiency of tramadol and morphine in managment of moderate pain in children after HSCT and ChT.

Patients and methods

The study included analysis of 159 children admitted to the ICU pain management team with complaints for weak or moderate pain (form 3 to 6 points on an age-matched scale). The age of patients was from 1 to 17 years, with a median of 8 years old. All the patients did not receive opioids (were opioid naïve) within 30 days before inclusion to the study. The drugs were injected by continuous infusion at the inpatient clinic. In the first group (n=118), standard tramadol doses were administered as the 1st-line therapy (0.2 to 0.3 mg/kg/h). The patients form 2nd group (n=41) were administered low-dose morphine (0.01 to 0.019 mg/kg/h). Treatment efficiency was assessed by FLACC verbal scores, Wong-Baker Faces Pain Rating Scale, or visual analogue scale and quality of life. Statistical evaluation was performed by means of SPSS software, using a nonparametric Chi-square criterion.

Results

When administered tramadol as a first-line therapy, it was efficient in ca. 40.7% of cases (n=48). With low-dose morphine, the response rate proved to be 58.5% (n=24). One patient (0.8%) received tramadol when transferred

to other institution. The second-line therapy (strong opioids) was administered due to lack of efficiency, or poor drug acceptability during the first-line treatment. It was observed in 53.4% of group 1 (n=63), and in 39% (n=16) of morphine-treated patients (group 2). Side effects due to tramadol administration were observed in 5.1% of cases (n=6). When administered low-dose morphine, only 1 female patient (2.4%) developed intestinal paresis which resolved after the therapy cancellation. Upon statistical evaluation, no significant differences were revealed between the groups.

Conclusion

Both medical drugs have shown similar efficiency and safety when applied for jugulating weak or moderate nociceptive pain after cytostatic chemotherapy and HSCT in pediatric patients.

Keywords

Chemotherapy, anticancer, pain syndrome, mucositis, tramadol, morphine, efficiency, safety.

Introduction

Survival rates of children and adolescents with oncological diseases significantly improved due to development of novel chemotherapy (ChT) protocols. In large part, this could be explained by more aggressive treatment, thus requiring a more careful selection of supportive and symptomatic therapy. Pain is among the most common symptoms which trouble both sick children themselves, and their parents [1].

Hematopoietic stem cell transplantation (HSCT) is a high-risk treatment aimed for therapy of both oncological, non-malignant hematological and some orphan diseases. Early post-transplant period is accompanied by such common conditions, e.g., weakness, pains and insomnia. These complaints are presented in 8 to 55% of autologous HSCTs [2], and 60 до 80% of allogeneic HSCT recipients [3]. Oral and gastrointestinal mucositis is among common painful complications occurring in 20 to 40% of chemotherapy (ChT) courses, and in up to 80% cases of conditioning treatment preceding HSCT, dependent on the drug combination applied [4].

Cytotoxic drugs used for conditioning therapy before allo-HSCT could damage endothelium of liver with subsequent development of veno-occlusive disease which could manifest with hepatomegaly accompanied by right upper quadrant pain due to extensive distension of Glisson capsule. This complication may encounter in 13.7% cases of HCST, as well as after ChT course [5]. In our experience, pain syndromes may be also connected with development of acute hemorrhagic cystitis, infections, fast engraftment, bone marrow necrosis, bone pain associated with corticosteroid withdrawal etc.

Thrombocytopenia, agranulocytosis, and, sometimes, renal dysfunction comprise special features in the patients after HSCT and some ChT regimens, thus limiting the opportunities for usage of nonsteroid anti-inflammatory drugs (NSAID), as first step of WHO analgetic ladder. Administration of these medicines as analgetics, could also hide fever of infectious origin. One should also note limited routes for administration of painkillers, i.e., per oral uptake could be difficult due to evolving mucositis. Rectal administration is not recommended, because of high-risk translocation of gut microflora in neutropenic conditions, whereas intramuscular injections are contraindicated, due to thrombocytopenia and painful manipulation [6, 7]. In this view, management of weak and moderate pain with NSAID may be difficult, and one should change the therapy for second-line treatment at early stages. Previously, WHO has excluded the second stage of pain relief ladder using weak opioids, e.g., codeine [7]. From 2009 to 2012, several cases of breath depression were registered in children under 5 years old after codeine postoperative analgesia after tonsillectomy. Most likely, this side effect was associated with individual genetic feature of cytochrome enzymes e.g., ultra-fast codeine activation by CYP2D6 with excessive production of morphine which, under normal excretion rates, could be accumulated at toxic concentrations.

In particular, tramadol is mostly inactivated by two enzymes, CYP2D6 and CYP3A4, whereas unchanged M1 metabolite, is, in turn, is excreted with urine. The analgetic effects of the drug are explained by, at least, two mechanisms, i.e., interaction between tramadol/M1 metabolite and μ-opiate receptors (OPRM1), as well as inhibition of serotonin and norepinephrine reuptake by tramadol, thus suppressing pain impulse transmission at the level of spinal cord [8, 9]. Undoubtedly, the patients with ultra-fast tramadol metabolism are in high-risk group, especially, in cases of high-dose treatment and appropriate comorbidities of respiratory system, sleep apnea in tonsillar hyperplasia, or obesity conditions [10]. Therefore, some authors recommend to admit the patients to inpatient unit as early as 24 hours before treatment, in cases of acute nociceptive pain in patients administered tramadol and uncertain CYP2D6 activity levels [11]. Concerning the analgetic capacity, tramadol takes an intermediate position between NSAID and potent opioids, but at the same time, some publications report on less common frequency of sedation, respiratory depression, constipation and other side effects typical to strong opioids [12]. At the present time, tramadol is widely used for treatment of nociceptive pain in traumas and after surgical interventions in children [13, 14, 15, 16, 17, 18]. For moderate pain, the WHO analgesia ladder presumes low doses of strong opioids (oxycodone or morphine) to be the main alternative for weak opioids.

High individual variability of efficient dose is a specific feature of morphine administration. This characteristic could be explained by differences in its bioavailability, metabolism and excretion. The main morphine metabolites are as follows: morphine-6-glucuronide, which exhibits higher

analgetic ability, but can elicit nausea, vomiting, excessive sedation, as well as morphime-3-glucuronide with probable antianalgetic and neurotoxic effects [19]. Several studies report about efficiency and safety of low-dose-morphine when managing moderate pain, e.g., in pediatric practice [20, 21, 22, 23]. In turn, the adverse effects of morphine derivatives are not shown at the present time (19).

Worth of note, however, both morphine and tramadol, may also display some side effects, including nausea, vomiting, respiratory depression, urinary retention, constipation, skin itching etc., thus causing discomfort to the patient [24, 25]. Therefore, the aim of our study was to evaluate efficiency and safety of tramadol and low-dose morphine in the treatment of moderate pain in children.

Patients and methods

The study was conducted in the Anesthesiology Department of R. M. Gorbacheva Memorial Institute for Pediatric Hematology, Oncology and Transplantation. The study included 159 primary admittances of the patients 1 to 17 years old (a median of 8 years) with complaints of moderate pain. Their age distribution is shown in Fig. 1.

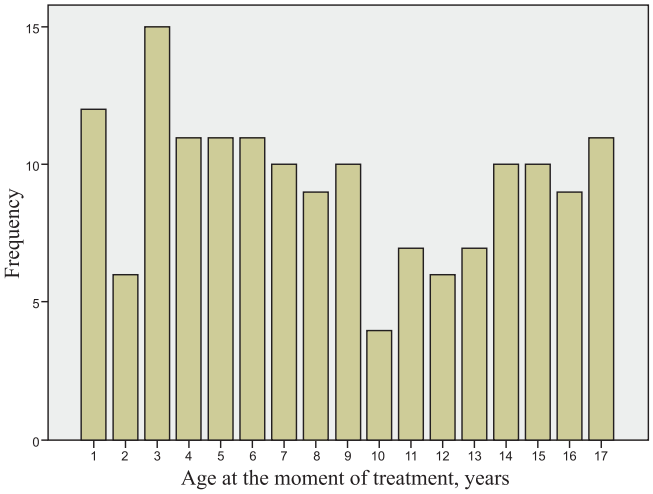

Figure 1. Patients age distribution

The diagnoses were as follows: solid malignancies, 55.4% (n=88); hemoblastoses, 35.2% (n=56); non-malignant hematological disorders, 5% (n=8) and orphan diseases 4.4% (n=7).

Of them, 13.8% (n=22) were subjected to ChT, 68.8% (n=109) underwent allo- or auto-HSCT with myeloablative treatment regimen; 17.6% (n=28) received HSCT with non-myeloablative conditioning. The main reasons for pain syndrome were: mucositis, 85.5% (n=136), bone pain associated with hematopoiesis recovery, 5% (n=8); progression of primary disease, 5% (n=8); intestinal graft-versus-host disease (GvHD) 1.3%, (n=2), mucositis combined with acute cystitis 2.5% (n=4); paraproctitis, 0.7% (n=1), as seen in Fig. 2.

The intensity if pain was evaluated 3 times a day throughout the observation period to age-matched scale adapted to abilities of the patient (FLACC, verbal scale, Wong-Baker Faces

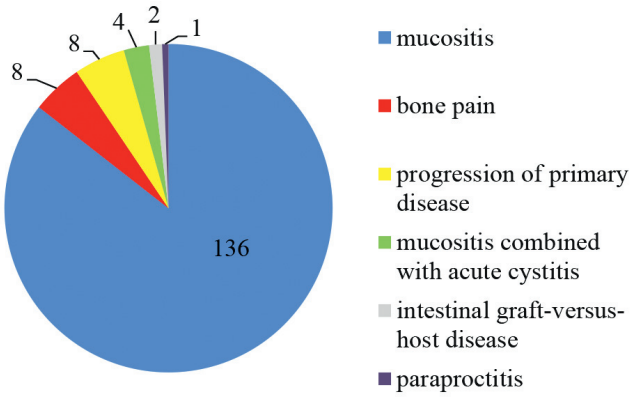

Figure 2. Distribution of main causes of pain

Pain Rating Scale, or visual analogue scale). The total time of observation, including, changing lines of analgesic therapy, if necessary, ranged from 1 to 20 days (median 6 days). The response to therapy was assessed integrally by such parameters as: pain intensity (permanent and activity-evoked), quality of night sleep, ability of food and drink intake without an pain related failure, the possibility of non-pharmacological treatment and patient satisfaction. All the patients were classified into 2 groups in a ratio 3:1. The drugs were injected by continuous infusion at the inpatient clinic. In the first group (n=118), standard tramadol doses were administered as the 1st-line therapy (0.2 to 0.3 mg/kg/h). The patients in the 2nd group (n=41) were administered low-dose morphine (0.01 to 0.019 mg/kg/h). The initially prescribed analgetic was the first line of therapy, if there was a change of therapy, then the new analgetic was considered the second line of therapy. Drug infusion was performed permanently, *via* central venous catheter under hospital conditions. Pain intensity and drug acceptability were evaluated 2-3 times a day. In cases of insufficient analgesia, i.e., non-reduced or enhanced pain, lack of food and fluid intake because of pain etc., the drug was changed, or morphine dosage was increased. The analgetics were also changed in case of bad tolerance of current therapy. The choice of drug was made individually, depending on clinical situation.

Statistical evaluation was performed by means of SPSS software, using Chi-square test. When checking statistical hypotheses, the difference was presumed significant by $p<0.05$.

Results

The results of our study have revealed that the therapy was effective in 40.7% (n=48) and 58.5% (n=24) for tramadol and low-dose morphine treatment respectively, whereas in 0.8% of the cases, tramadol administration was prolonged to the end of staying in the unit/transfer to hospice, with good therapy acceptability. Enhanced analgetic treatment was required in 53.4% (n=63) for the 1st group *versus* 39.0% (n=16) for the patients in the 2nd group (Table 1).

Adverse effects in the first (tramadol-treated) group were observed in 5.1% (n=6). In particular, we observed one case of somnolescence with subsequent excitation in a girl of 4 years old; one case of dizziness with tremor in a girl of 11 years old. Two cases of involuntary contractions of striated muscles

Table 1. First line therapy results

1st line of analgetic therapy		Result			
		Good response to therapy	Transfer to hospice	Switch for the 2nd line therapy	
				Poor response to therapy	Adverse effects
Tramadol	Number of patients	**48**	**1**	**63**	**6**
	Percentage of patients in the group (n=118)	**40.7%**	**0.8%**	**53.4%**	**5.1%**
Low dose morphine	Number of patients	**24**	**0**	**16**	**1**
	Percentage of patients in the group (n=41)	**58.5%**	**0.0%**	**39.0%**	**2.5%**
Total	Number of patients	**72**	**1**	**79**	**7**
	Percentage of patients in the group (n=159)	**45.3%**	**0.6%**	**49.7%**	**4.4%**

were detected: a 6 years old girl had twitching of right hand by 2 days after tramadol injections, and a 10 years old boy developed involuntary contractions of mimic muscles after 3 days of treatment, probably, due to serotoninergic effect of the drug. We have also seen one case of vomiting and nausea in the 17 years old female, as well as a case of nausea and anxiety in the 16 years old female. At the next treatment courses, this pain management was based on strong opioids. Their injection was accompanied by similar side effects. However, the mentioned side effects were no health-threatening. Subsequently 6 years old girl required the change of therapy to fentanyl. In other cases after cancellation of tramadol infusion, weak pain persisted, but further analgesia was not necessary. In the second group, only one female patient (2.4% of total) treated with low-dose morphine developed intestinal paralysis that was resolved after the therapy change.

Upon statistical analysis with Chi-square method, no significant differences were found between the tramadol group and low-dose morphine-treated groups in effectiveness and frequency of side effects (p=0.237).

In case of inefficiency of tramadol or low doses of morphine the second line of therapy included morphine in a low dose (after tramadol administration) was used in 29.1% (n=23), morphine in a standard dose (from 0.02 mg/kg/hr) in 17.7% (n=14) or fentanyl at a dose of 0.05 mcg/kg/hr in 53.2% (n=42) (Table 2).

We also evaluated the safety of low and standard doses of morphine in the second line of pain management therapy (Table 3). As result, we observed that side effects appeared in two cases: one because of nausea and vomiting and one due to complaints of blurred focus of vision, which was possibly associated with myosis. In group of standard doses of morphine one case of postrenal urinary retention. All three cases required a revision of treatment.

Upon statistical analysis with Chi-square method, no significant differences were found between the standard and low-dose morphine-treated patients in effectiveness and frequency of side effects (p=0.271).

Table 2. Distribution of the 2nd line therapy medicines

Patients		2nd line therapy medicines		
		Morphine		Fentanyl
		Low dose	Standard dose	
Tramadol group	Number of patients, switched to 2nd line therapy	23	10	30
	Percentage of total number of patients, in the group switched to 2nd line therapy (n=63)	36.5%	15.9%	47.6%
Low dose morphine group	Number of patients, switched to 2nd line therapy	0	4	12
	Percentage of total number of patients, in the group switched to 2nd line therapy (n=16)	0.0%	25.0%	75.0%
Total	Number of patients, switched to 2nd line therapy	23	14	42
	Percentage of total number of patients, in the group switched to 2nd line therapy (n=79)	29.1%	17.7%	53.2%

Table 3. Results of second line therapy with morphine in low and standard doses

2nd line of analgetic therapy		Result			
		Good response to therapy	Switch to tramadol (due to pain reduce)	Switch for the 3rd line therapy	
				Poor response to therapy	Adverse effects
Low dose morphine	Number of patients	**14**	**0**	**7**	**2**
	Percentage of patients in the group (n=23)	**60.9%**	**0%**	**30.4%**	**8.7%**
Standard dose morphine	Number of patients	**6**	**2**	**5**	**1**
	Percentage of patients in the group (n=14)	**42.9%**	**14.3%**	**35.7%**	**7.1%**
Total	Number of patients	**20**	**2**	**12**	**3**
	Percentage of patients in the group (n=159)	**54.1%**	**5.4%**	**32.4%**	**8.1%**

Discussion

Currently, some authors state that the respiratory depression is rarely encountered when tramadol dosage is carefully maintained [26, 27]. Frequency of nausea and vomiting are compatible (10-40%) when administering tramadol or opioids [28]. In our experience, a case of intestinal paralysis should be noted in a female patient from 2nd group with mucositis. She had also side effects in the course of immune suppressors (nephro- and neurotoxicity), as well as pancytopenia and hemorrhagic syndrome that could be risk factors of this condition. Concerning adverse effects associated with tramadol prescription, the literature presents only single cases of generalized cramps due to excessive dosage and drug administration to a child under 1 year old [29]. One may also suggest an evolving serotonin syndrome connected to high dosage of serotoninergic drugs (selective serotonin reuptake inhibitors, some monoamine oxidase inhibitors), which includes excitation, ataxia, increased sweating, diarrhea, fever, hyperreflexia, and tremor. In our study, similar symptoms were seen in 4 patients, however, at less significant. This is, probably, connected with non-opioid effects of the drug (inhibition of serotonin and norepinephrin reuptake) [30, 31]. However, one cannot exclude ultra-fast CYP2D6 activity. That is the key aspects influencing tramadol efficiency and, potentially, genetic studies could serve as a predictor of efficacy and safety of the drug. Meanwhile, the CYP2D6 gene polymorphism is quite variable and requires time-consuming molecular genetic studies, thus reducing value of this technique in case of acute pain. One should also understand that the genotype will correspond to phenotype, with regard to variable clearance and body weight [8]. Therefore, we observe the children at the hospital within first 24 hours after starting tramadol infusion. For the patients requiring longer analgesia period, than in our study, tramadol shows lesser potential risk of dependence compared to classical opioids [32]. It's also important to note that administration of tramadol has a less strict legal regulation [33, 34]. Due to social prejustice, its administration causes lesser anxiety on the part of parents and adolescent patients with respect to adverse effects, ex., addiction. Similarly, in cases with inefficiency of this therapy, the parents take easier administration of strong opioids [35, 36]. In future, tapentadol and local morphine applications could be promising therapeutic options [37]. However, there are only modest data on the studies of these medications in children and adolescents.

Conclusions

Based on the study data, we may suggest that tramadol exerts analgetic effects which are comparable to low-dose morphine. However, administration of these drugs needs dynamic observation of pediatric patients in the hospital at initial steps of therapy, due to some features of individual response and probable side effects. These issues also require further studies in larger groups of patients.

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Conflict of interests

The authors declare no conflicts of interest.

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Оценка эффективности и безопасности трамадола и морфина в низких дозах при купировании боли у детей после проведения химиотерапии и трансплантации гемопоэтических стволовых клеток

Екатерина В. Гончарова [1,2], Инга Е. Заводова [1], Никита П. Волков [1], Ольга А. Иванова [1], Максим А. Кучер[1], Алексей Ю. Соколов [2,3], Максим П. Богомольный [1], Глеб Э. Ульрих [4], Людмила С. Зубаровская [1], Борис В. Афанасьев [1]

[1] НИИ детской онкологии, гематологии и трансплантологии им. Р. М. Горбачевой, Первый Санкт-Петербургский государственный медицинский университет им. акад. И. П. Павлова, Санкт-Петербург, Россия
[2] Отдел нейрофармакологии Института фармакологии им. А. В. Вальдмана ПСПбГМУ им. акад. И. П. Павлова, Санкт-Петербург, Россия
[3] Институт физиологии им. И. П. Павлова Российской академии наук, Санкт-Петербург, Россия
[4] Кафедра анестезиологии, реаниматологии и неотложной педиатрии Санкт-Петербургского государственного педиатрического медицинского университета, Санкт-Петербург, Россия

Резюме

Во время и после проведения полихимиотерапии (ПХТ) с последующей трансплантацией гемопоэтических стволовых клеток (ТГСК) или без нее значительная часть пациентов сталкивается с развитием болевого синдрома различных интенсивности и этиологии. В этот период у пациента может отмечаться тромбоцитопения и лейкопения, вплоть до агранулоцитоза, что ограничивает назначение нестероидных противовоспалительных препаратов (НПВП). В соответствии с рекомендациями ВОЗ при развитии боли умеренной интенсивности и неэффективности НПВП в педиатрической практике возможно назначение опиоидов. При этом не исключается использование трамадола, который в настоящее время, благодаря облегченному правовому регулированию, широко применяется клинической практике. Цель – оценить безопасность и эффективность трамадола и морфина в низких дозах при купировании умеренной ноцицептивной боли различной этиологии у детей после ТГСК и ПХТ.

Материалы и методы

В исследование включено 159 пациентов с жалобами на боль различной локализации интенсивностью от 3 до 6 баллов по шкале оценки, соответствующей возрасту и возможностям ребенка. Возраст детей составлял от 1 до 17 лет (медиана 8 лет). Все пациенты не получали опиоиды за 30 суток до включения в исследование (opioid naïve). Препараты вводили внутривенно посредством круглосуточной микроструйной инфузии в условиях стационара. В первой группе (n=118), в качестве терапии 1 линии назначался трамадол в стандартных дозах (от 0,2 до 0,3 мг/кг/час). Участники второй группы (n=41), получали морфин в низких дозах (от 0,01 до 0,019 мг/кг/час). Эффективность терапии оценивалась по совокупности факторов: снижение интенсивности боли до удовлетворительной для пациента, отсутствие ночных пробуждений, связанных с болью, отсутствие препятствий к приему пищи и/или жидкости в виде болевых ощущений и др. Безопасность оценивалась по наличию или отсутствию побочных эффектов, связанных с назначенными препаратами. Статистическая обработка проводилась в программе SPSS, для определения значимости различий использовался критерий согласия X2.

Результаты

Трамадол был эффективен в 40,7% случаев (n=48), низкие дозы морфина – в 58,5% (n=24).

Назначение 2-й линии терапии, связанное с неэффективностью или плохой переносимостью препаратов первой линии, потребовалось в 1 группе у 53,4% пациентов (n=63), и у 39% (n=16) – во 2 группе. Побочные эффекты, связанные с назначением трамадола, возникли в 5.1% случаев (n=6). В группе морфина у 1 пациентки (2,4%) развился парез кишечника, разрешившийся после смены терапии. При статистическом анализе значимых межгрупповых различий с точки зрения эффективности и безопасности лечения выявлено не было.

Выводы

Оба препарата в сравниваемых дозах показали схожие эффективность и безопасность при купировании умеренной боли у детей после проведения ПХТ и ТГСК.

Ключевые слова

Химиотерапия, противоопухолевая, болевой синдром, мукозиты, трамадол, морфин, эффективность, безопасность.